

Lopinavir; Ritonavir

Indications/Dosage

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Labeled

- human immunodeficiency virus (HIV) infection

Off-Label

- coronavirus disease 2019 (COVID-19) †
- human immunodeficiency virus (HIV) prophylaxis †
- severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection †

† Off-label indication

NOTE: HIV guidelines recommend consideration be given to avoiding use of lopinavir; ritonavir-containing regimens in patients at high risk for cardiovascular adverse events.[\[46638\]](#)

Initiation of therapy for HIV treatment: [\[46638\]](#) [\[23512\]](#) [\[42452\]](#)

- For adults, initiation of treatment immediately (or as soon as possible) after HIV diagnosis is recommended in all patients to reduce the risk of disease progression and to prevent the transmission of HIV, including perinatal transmission and transmission to sexual partners. Starting antiretroviral therapy early is particularly important for patients with AIDS-defining conditions, those with acute or recent HIV infection, and individuals who are pregnant; delaying therapy in these subpopulations has been associated with high risks of morbidity, mortality, and HIV transmission.
- Antiretroviral drug-resistance testing:
 - Genotypic drug-resistance testing is recommended prior to initiation of therapy in all antiretroviral treatment-naïve patients and prior to changing therapy for treatment failure.
 - Phenotypic resistance testing may be used in conjunction with the genotypic test for patients with known or suspected complex drug-resistance mutation patterns.
 - HIV-1 proviral DNA resistance testing is available for use in patients with HIV RNA concentrations below the limits of detection or with low-level viremia (i.e., less than 1,000 copies/mL), where genotypic testing is unlikely to be successful; however, the clinical utility of this assay has not been fully determined.
- Pediatric guidelines are also available.

Place in therapy for HIV treatment: [\[46638\]](#) [\[23512\]](#) [\[42452\]](#)

- Lopinavir; ritonavir (twice daily) given in combination with 2 NRTIs is an alternative protease inhibitor-based treatment regimen for pregnant adults and adolescents with HIV-1, HIV-2, or HIV-1/HIV-2 coinfection. Once-daily lopinavir; ritonavir is NOT recommended for use during pregnancy.
- Due to a high pill burden and low tolerability, use of this drug as part of an initial HIV-1 treatment regimen for non-pregnant, treatment-naïve adults and adolescents is no longer recommended.
- Lopinavir; ritonavir plus 2 NRTIs is also an alternative initial regimen for some non-pregnant patients who have HIV-2 monoinfection or HIV-1/HIV-2 coinfection.
- Pediatric guidelines are also available.

Per the manufacturer, this drug has been shown to be active against most strains of the following microorganisms either in vitro and/or in clinical infections:

human immunodeficiency virus (HIV).

NOTE: The safety and effectiveness in treating clinical infections due to organisms with in vitro data only have not been established in adequate and well-controlled clinical trials.

This drug may also have activity against the following microorganisms:

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

NOTE: Some organisms may not have been adequately studied during clinical trials; therefore, exclusion from this list does not necessarily negate the drug's activity against the organism.

For the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents

NOTE: The following abbreviations are used: nucleoside reverse transcriptase inhibitors (NRTIs); nonnucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PIs).

NOTE: Lopinavir, ritonavir should not be administered once daily in pediatric patients due to inferior efficacy observed with once daily dosing compared with twice daily dosing.[\[28341\]](#)

Oral dosage (tablets)

- **Adults**

400 mg/100 mg PO twice daily. Alternatively, 800 mg/200 mg PO once daily may be administered to patients with less than 3 lopinavir resistance-associated substitutions.[\[28341\]](#) NOTE: See dosing below for concomitant efavirenz, nelfinavir, nevirapine, carbamazepine, phenobarbital, or phenytoin therapy.

- **Adult pregnant females**

400 mg/100 mg PO twice daily in patients with no documented lopinavir resistance-associated substitutions; there are insufficient data to recommend dosing in pregnant women with any lopinavir resistance-associated substitutions.[\[28341\]](#) HIV guidelines suggest increasing dose to 500 mg/125 mg or 600 mg/150 mg PO twice daily may be necessary in the 2nd and 3rd trimesters, especially for PI-experienced women and women with baseline viral loads more than 50 copies/mL. Once daily dosing is NOT recommended.[\[28341\]](#) [\[23512\]](#)

- **Children and Adolescents weighing more than 35 kg**

400 mg/100 mg PO twice daily (for a BSA target of 300 mg/75 mg per m²/dose or 230 mg/57.5 mg per m²/dose).[\[28341\]](#) [\[42452\]](#) NOTE: See dosing below for concomitant efavirenz, nelfinavir, or nevirapine therapy.

- **Children and Adolescents weighing 31 to 35 kg**

400 mg/100 mg PO twice daily (for a BSA target of 300 mg/75 mg per m²/dose) or 300 mg/75 mg PO twice daily (for a BSA target of 230 mg/57.5 mg per m²/dose).[\[28341\]](#) [\[42452\]](#) NOTE: See dosing below for concomitant efavirenz, nelfinavir, or nevirapine therapy.

- **Children weighing 26 to 30 kg**

300 mg/75 mg PO twice daily (for a BSA target of 300 mg/75 mg per m²/dose or 230 mg/57.5 mg per m²/dose).[\[28341\]](#) [\[42452\]](#) NOTE: See dosing below for concomitant efavirenz, nelfinavir, or nevirapine therapy.

- **Children weighing 21 to 25 kg**

300 mg/75 mg PO twice daily (for a BSA target of 300 mg/75 mg per m²/dose) or 200 mg/50 mg PO twice daily (for a BSA target of 230 mg/57.5 mg per m²/dose).[\[28341\]](#) [\[42452\]](#) NOTE: See dosing below for concomitant efavirenz, nelfinavir, or nevirapine

- **Children weighing 15 to 20 kg**

200 mg/50 mg PO twice daily (for a BSA target of 300 mg/75 mg per m²/dose or 230 mg/57.5 mg per m²/dose).[\[28341\]](#) [\[42452\]](#) NOTE: See dosing below for concomitant efavirenz, nelfinavir, or nevirapine therapy.

- **Adults receiving concomitant carbamazepine, phenobarbital, or phenytoin**

400 mg/100 mg PO twice daily. Do NOT administer once daily dosing.[\[28341\]](#)

- **Adults receiving concomitant efavirenz, nelfinavir, or nevirapine**

500 mg/125 mg PO twice daily. Some experts would use 600 mg/150 mg PO twice daily for ease of tablet dosing.[\[28341\]](#) [\[42452\]](#)

- **Children and Adolescents weighing more than 45 kg receiving concomitant efavirenz, nelfinavir, or nevirapine**

500 mg/125 mg PO twice daily. Some experts would use 600 mg/150 mg PO twice daily for ease of tablet dosing.[\[28341\]](#) [\[42452\]](#)

- **Children and Adolescents weighing 31 to 45 kg receiving concomitant efavirenz, nelfinavir, or nevirapine**

400 mg/100 mg PO twice daily.[\[28341\]](#) [\[42452\]](#)

- **Children weighing 21 to 30 kg receiving concomitant efavirenz, nelfinavir, or nevirapine**

300 mg/75 mg PO twice daily.[\[28341\]](#) [\[42452\]](#)

- **Children weighing 15 to 20 kg receiving concomitant efavirenz, nelfinavir, or nevirapine**

200 mg/50 mg PO twice daily.[\[28341\]](#) [\[42452\]](#)

Oral dosage (oral solution)

- **Adults**

400 mg/100 mg PO twice daily. Alternatively, 800 mg/200 mg PO once daily may be administered to patients with less than 3 lopinavir resistance-associated substitutions. The oral solution should be avoided during pregnancy due to the alcohol content.[\[28341\]](#) [\[51080\]](#) NOTE: See dosing below for concomitant efavirenz, nelfinavir, nevirapine, carbamazepine, phenobarbital, or phenytoin therapy.

- **Children and Adolescents**

300 mg/75 mg per m²/dose PO twice daily is routinely used by many clinicians, especially for treatment-experienced patients; however, 230 mg/57.5 mg per m²/dose PO twice daily can be used for antiretroviral-naïve patients.[\[42452\]](#) The manufacturer recommends 230 mg/57.5 mg per m²/dose PO twice daily. Alternatively, a weight based dose of 12 mg/3 mg per kg/dose PO twice daily for patients weighing less than 15 kg or 10 mg/2.5 mg per kg/dose PO twice daily for patients weighing 15 kg or more may be used. The maximum recommended dose is 400 mg/100 mg per dose.[\[28341\]](#) NOTE: See dosing below for concomitant efavirenz, nelfinavir, or nevirapine therapy.

- **Infants 7 to 11 months**

300 mg/75 mg per m²/dose PO twice daily is recommended by the HIV guidelines.[\[42452\]](#) The manufacturer, however, recommends 230 mg/57.5 mg per m²/dose PO twice daily. Alternatively, a weight based dose of 12 mg/3 mg per kg/dose PO twice daily for patients weighing less than 15 kg or 10 mg/2.5 mg per kg/dose PO twice daily for patients weighing 15 kg or more may be used.[\[28341\]](#) Adjust doses frequently to accommodate growth. NOTE: See dosing below for concomitant efavirenz, nelfinavir, or nevirapine therapy.

- **Neonates 14 to 29 days postnatal age and 42 weeks postmenstrual age or older and Infants 1 to 6 months**

300 mg/75 mg per m²/dose PO twice daily. Alternatively, a weight-based dose of 16 mg/4 mg per kg/dose PO twice daily may also be used. Adjust doses frequently to accommodate growth. Be aware of alcohol and propylene glycol intake; oral solution contains 42.4% (v/v) alcohol and 15.3% (w/v) propylene glycol.[\[28341\]](#) [\[42452\]](#) NOTE: See dosing below for concomitant efavirenz, nelfinavir, or nevirapine therapy.

- **Neonates 0 to 13 days postnatal age or younger than 42 weeks postmenstrual age**

Use in this patient population is not recommended because of the potential for toxicities.[\[28341\]](#) [\[42452\]](#)

- **Adults receiving concomitant carbamazepine, phenobarbital, or phenytoin**

400 mg/100 mg PO twice daily. Do NOT administer once daily dosing.[\[28341\]](#)

- **Adults receiving concomitant efavirenz, nelfinavir, or nevirapine**

520 mg/130 mg PO twice daily.[\[28341\]](#)

- **Children and Adolescents weighing more than 45 kg receiving concomitant efavirenz, nelfinavir, or nevirapine**

520 mg/130 mg PO twice daily.[\[28341\]](#) [\[42452\]](#)

- **Infants 7 to 11 months, Children, and Adolescents weighing 15 to 45 kg receiving concomitant efavirenz, nelfinavir, or nevirapine**

11 mg/2.75 mg per kg/dose (or 300 mg/75 mg per m²/dose) PO twice daily.[\[28341\]](#) [\[42452\]](#)

- **Infants 7 to 11 months and Children weighing less than 15 kg receiving concomitant efavirenz, nelfinavir, or nevirapine**

13 mg/3.25 mg per kg/dose (or 300 mg/75 mg per m²/dose) PO twice daily.[\[28341\]](#) [\[42452\]](#)

- **Neonates 14 to 29 days postnatal age and 42 weeks postmenstrual age or older and Infants 1 to 6 months receiving concomitant efavirenz, nelfinavir, or nevirapine**

Lopinavir; ritonavir is not recommended in combination with these drugs.[\[28341\]](#)

For human immunodeficiency virus (HIV) prophylaxis†

for human immunodeficiency virus (HIV) prophylaxis† after occupational exposure

Oral dosage

• Adults

The World Health Organization (WHO) recommends lopinavir; ritonavir 400 mg/100 mg PO twice daily in combination with tenofovir and either emtricitabine or lamivudine as preferred HIV post-exposure prophylaxis (PEP) regimens. Alternative lopinavir; ritonavir dosing is 800 mg/200 mg PO once daily.[\[60431\]](#) The US Public Health Service guidelines and the New York State Department of Health AIDS Institute (NYSDOH AI) recommend lopinavir; ritonavir with either tenofovir or zidovudine and either emtricitabine or lamivudine as alternative PEP regimens. According to PEP guidelines, individuals potentially exposed to HIV should receive a 3-drug regimen for a total of 28 days; however if tolerability is a concern, use of a 2-drug regimen may be considered and is preferred to prophylaxis discontinuation. Begin prophylaxis as soon as possible, ideally within 2 hours of exposure. If initiation of prophylaxis is delayed (beyond 36 hours or 72 hours after exposure), efficacy of the antiretroviral regimen may be diminished and treatment should be determined on a case-by-case basis.[\[55597\]](#) [\[60367\]](#) [\[60431\]](#) Exposures for which PEP is indicated include: skin puncture by a sharp object that has been contaminated with blood, body fluid, or other infectious material; bite from a patient with visible bleeding in the mouth which causes bleeding by the exposed worker; splash of blood, body fluid, or other infectious material onto the workers mouth, nose, or eyes; exposure of blood, body fluid, or other infectious material on a workers non-intact skin (i.e., open wound, chapped skin, abrasion, dermatitis).[\[55597\]](#) [\[60367\]](#)

for human immunodeficiency virus (HIV) prophylaxis† after nonoccupational exposure, including sexual assault

NOTE: Higher risk exposures for which prophylaxis is recommended include exposure of vagina, rectum, eye, mouth, or other mucous membrane, nonintact skin, or percutaneous contact with blood, semen, vaginal secretions, rectal secretions, breast milk, or any body fluid that is visibly contaminated with blood when the source is known to be HIV-positive. Exposures to a source patient with unknown HIV status should be assessed on a case-by-case basis.[\[61819\]](#)

Oral dosage (solution)

• Children weighing more than 40 kg

400 mg/100 mg PO twice daily for 28 days in combination with tenofovir and emtricitabine or zidovudine and lamivudine is an alternative HIV post-exposure prophylaxis (PEP) regimen in children 2 years and older. A 3-drug regimen is recommended for all cases when PEP is indicated; however, the use of a 2-drug regimen (2 NRTIs or a combination of a PI and a NNRTI) may be considered if tolerability or adherence is a concern. Begin prophylaxis as soon as possible after exposure; prophylaxis initiated more than 72 hours after exposure is unlikely to be effective.[\[61819\]](#)

• Children 2 years and older weighing 15 to 40 kg

10 mg/2.5 mg per kg/dose PO twice daily for 28 days in combination with tenofovir and emtricitabine or zidovudine and lamivudine is an alternative HIV post-exposure prophylaxis (PEP) regimen in children 2 years and older. A 3-drug regimen is recommended for all cases when PEP is indicated; however, the use of a 2-drug regimen (2 NRTIs or a combination of a PI and a NNRTI) may be considered if tolerability or adherence is a concern. Begin prophylaxis as soon as possible after exposure; prophylaxis initiated more than 72 hours after exposure is unlikely to be effective.[\[61819\]](#)

• Children 2 years and older weighing less than 15 kg

12 mg/3 mg per kg/dose PO twice daily for 28 days in combination with tenofovir and emtricitabine or zidovudine and lamivudine is an alternative HIV post-exposure prophylaxis (PEP) regimen in children 2 years and older. A 3-drug regimen is recommended for all cases when PEP is indicated; however, the use of a 2-drug regimen (2 NRTIs or a combination of a PI and a NNRTI) may be considered if tolerability or adherence is a concern. Begin prophylaxis as soon as possible after exposure; prophylaxis initiated more than 72 hours after exposure is unlikely to be effective.[\[61819\]](#)

• Infants and Children 4 weeks to 1 year

300 mg/75 mg per m²/dose or 16 mg/4 mg per kg/dose PO twice daily for 28 days in combination with zidovudine and lamivudine is a preferred HIV post-exposure prophylaxis (PEP) regimen in infants and children younger than 2 years. Lopinavir/ritonavir in combination with zidovudine and emtricitabine is an alternative regimen. A 3-drug regimen is recommended for all cases when PEP is indicated; however, the use of a 2-drug regimen (2 NRTIs or a combination of a PI and a NNRTI) may be considered if tolerability

or adherence is a concern. Begin prophylaxis as soon as possible after exposure; prophylaxis initiated more than 72 hours after exposure is unlikely to be effective.[\[61819\]](#)

Oral dosage (tablets)

- **Children weighing more than 35 kg**

400 mg/100 mg PO twice daily for 28 days in combination with tenofovir and emtricitabine or zidovudine and lamivudine is an alternative HIV post-exposure prophylaxis (PEP) regimen in children 2 years and older. A 3-drug regimen is recommended for all cases when PEP is indicated; however, the use of a 2-drug regimen (2 NRTIs or a combination of a PI and a NNRTI) may be considered if tolerability or adherence is a concern. Begin prophylaxis as soon as possible after exposure; prophylaxis initiated more than 72 hours after exposure is unlikely to be effective.[\[61819\]](#)

- **Children weighing 26 to 35 kg**

300 mg/75 mg PO twice daily for 28 days in combination with tenofovir and emtricitabine or zidovudine and lamivudine is an alternative HIV post-exposure prophylaxis (PEP) regimen in children 2 years and older. A 3-drug regimen is recommended for all cases when PEP is indicated; however, the use of a 2-drug regimen (2 NRTIs or a combination of a PI and a NNRTI) may be considered if tolerability or adherence is a concern. Begin prophylaxis as soon as possible after exposure; prophylaxis initiated more than 72 hours after exposure is unlikely to be effective.[\[61819\]](#)

- **Children 2 years and older weighing 15 to 25 kg**

200 mg/50 mg PO twice daily for 28 days in combination with tenofovir and emtricitabine or zidovudine and lamivudine is an alternative HIV post-exposure prophylaxis (PEP) regimen in children 2 years and older. A 3-drug regimen is recommended for all cases when PEP is indicated; however, the use of a 2-drug regimen (2 NRTIs or a combination of a PI and a NNRTI) may be considered if tolerability or adherence is a concern. Begin prophylaxis as soon as possible after exposure; prophylaxis initiated more than 72 hours after exposure is unlikely to be effective.[\[61819\]](#)

INVESTIGATIONAL USE: For the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection†, the virus that causes coronavirus disease 2019 (COVID-19)†

Oral dosage

- **Adults**

Available data are limited and inconclusive. Due to unfavorable pharmacodynamics and negative clinical trial data, the National Institutes of Health (NIH) COVID-19 treatment guidelines recommend against the use of lopinavir; ritonavir outside of clinical trials. [\[65314\]](#) Lopinavir 400 mg/ritonavir 100 mg PO twice daily for 10 to 14 days is being evaluated alone and in combination based on use in retrospective cohorts, historically controlled studies, case reports, and case series for other coronavirus infections, including severe acute respiratory syndrome-associated coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Some low-level evidence suggests use may reduce the incidence or mortality associated with acute respiratory distress syndrome (ARDS).[\[65116\]](#) [\[65117\]](#) [\[65118\]](#) [\[65123\]](#) However, in a retrospective cohort study of hospitalized patients, no difference was noted in the duration of viral shedding after treatment with lopinavir; ritonavir (n = 29).[\[65146\]](#) Additionally, in a randomized, controlled, open-label trial involving hospitalized patients with confirmed SARS-CoV-2 infection (n = 199), treatment with lopinavir; ritonavir for 14 days was not associated with a difference from standard of care in the time to clinical improvement (hazard ratio 1.24; 95% CI, 0.9 to 1.72). Mortality at 28 days was similar between groups (19.2% vs. 25%, respectively). The percentages of patients with detectable viral RNA were similar. In a modified ITT analysis, lopinavir; ritonavir had a median time to clinical improvement that was shorter by 1 day (hazard ratio, 1.39%; 95% CI, 1 to 1.91).[\[65144\]](#) The role of lopinavir; ritonavir in the treatment of COVID-19 is unclear at this time.

Therapeutic Drug Monitoring

Suggested target trough concentration: 5,500 ng/mL

- Routine monitoring of plasma concentrations of antiretroviral (ARV) drugs is generally not recommended in HIV-infected patients. However, therapeutic drug monitoring may be considered in the following situations [\[42452\]](#)[\[46638\]](#):
 - use of drugs with significant food and/or drug interactions
 - suboptimal treatment response
 - suspected suboptimal absorption, distribution, metabolism, or elimination of the drug
 - suspected concentration-dependent drug-associated toxicity
 - use of alternative dosing regimens and ARV combinations for which safety and efficacy have not been established in clinical trials

- heavily pretreated patients experiencing virologic failure and who may have viral isolates with reduced susceptibility to ARVs
- pregnant patients who have risk factors for virologic failure, particularly during the later stages of pregnancy
- use of drugs in children with limited pharmacokinetic data and/or therapeutic experience

Maximum Dosage Limits

NOTE: The following maximum dosage limits apply for typical lopinavir; ritonavir use; maximum dosage limits may be altered based on certain individual patient circumstances, such as in the case of specific drug interactions.

- Adults

800 mg/200 mg per day PO.

- Geriatric

800 mg/200 mg per day PO.

- Adolescents

more than 40 kg: 800 mg/200 mg per day.

36 to 40 kg: 800 mg/200 mg per day PO for tablets; 20 mg/5 mg per kg/day or 460 mg/115 mg per m²/day PO for oral solution is recommended in the FDA-approved labeling; however, up to 600 mg/150 mg per m²/day for oral solution (Max: 800 mg/200 mg per day) is recommended in the HIV guidelines.

31 to 35 kg: 600 mg/150 mg per day PO for tablets; 20 mg/5 mg per kg/day or 460 mg/115 mg per m²/day PO for oral solution is recommended in the FDA-approved labeling; however, up to 600 mg/150 mg per m²/day oral solution or 800 mg/200 mg per day for oral tablets is recommended in the HIV guidelines.

- Children

more than 40 kg: 800 mg/200 mg per day PO.

36 to 40 kg: 800 mg/200 mg per day PO for tablets; 20 mg/5 mg per kg/day or 460 mg/115 mg per m²/day PO for oral solution is recommended in the FDA-approved labeling; however, up to 600 mg/150 mg per m²/day for oral solution (Max: 800 mg/200 mg per day) is recommended in the HIV guidelines.

31 to 35 kg: 600 mg/150 mg per day PO for tablets; 20 mg/5 mg per kg/day or 460 mg/115 mg per m²/day PO for oral solution is recommended in the FDA-approved labeling; however, up to 600 mg/150 mg per m²/day for oral solution or 800 mg/200 mg per day for oral tablets is recommended in the HIV guidelines.

26 to 30 kg: 600 mg/150 mg per day PO for tablets; 20 mg/5 mg per kg/day or 460 mg/115 mg per m²/day PO for oral solution is recommended in the FDA-approved labeling; however, up to 600 mg/150 mg per m²/day oral solution is recommended in the HIV guidelines.

21 to 25 kg: 400 mg/100 mg per day PO for tablets; 20 mg/5 mg per kg/day or 460 mg/115 mg per m²/day PO for oral solution is recommended in the FDA-approved labeling; however, up to 600 mg/150 mg per m²/day for oral solution or 600 mg/150 mg per day for oral tablets is recommended in the HIV guidelines.

15 to 20 kg: 400 mg/100 mg per day PO for tablets; 20 mg/5 mg per kg/day or 460 mg/115 mg per m²/day PO for oral solution is recommended in the FDA-approved labeling; however, up to 600 mg/150 mg per m²/day for oral solution is recommended in the HIV guidelines.

less than 15 kg: 24 mg/6 mg per kg/day or 460 mg/115 mg per m²/day PO for oral solution is recommended in the FDA-approved labeling; however, up to 600 mg/150 mg per m²/day is recommended in the HIV guidelines. Safety and efficacy of the tablet formulation have not been established.

- Infants

older than 6 months: 24 mg/6 mg per kg/day PO or 460 mg/115 mg per m²/day PO for oral solution is recommended in the FDA-approved labeling; however, up to 600 mg/150 mg per m²/day is recommended in the HIV guidelines. Safety and efficacy of the tablet formulation have not been established.

6 months or younger: 32 mg/8 mg per kg/day PO or 600 mg/150 mg per m²/day PO for oral solution. Safety and efficacy of the tablet formulation have not been established.

- Neonates

14 days postnatal age or older and 42 weeks postmenstrual age or older: 32 mg/8 mg per kg/day PO or 600 mg/150 mg per m²/day PO for oral solution. Safety and efficacy of other formulations have not been established.

younger than 14 days or postmenstrual age younger than 42 weeks: Not recommended.

Patients with Hepatic Impairment Dosing

Lopinavir is metabolized by the liver. Use caution and close monitoring when administering to patients with mild to moderate hepatic impairment (Child-Pugh A and B), as increased drug concentrations may occur. Use in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated.^[28341]

Patients with Renal Impairment Dosing

Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.^[28341]

Intermittent Hemodialysis

Avoid once-daily dosing in patients on hemodialysis.^[46638]

† Off-label indication

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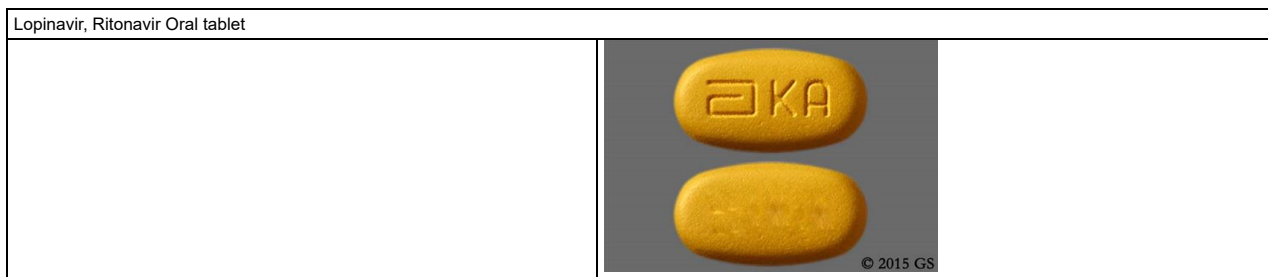
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How Supplied

Lopinavir, Ritonavir Oral capsule	
<p>Kaletra 133.3mg-33.3mg Capsule (00074-3959) (AbbVie US LLC) (off market)</p>	 <p>© 2005 GS</p>
Lopinavir, Ritonavir Oral solution	
<p>Kaletra 80mg-20mg/mL Solution (00074-3956) (AbbVie US LLC)</p>	 <p>© 2016 GS © 2005 GS</p>
<p>Lopinavir/Ritonavir 80mg-20mg/mL Solution (00527-1947) (Lannett Company, Inc.)</p>	
Lopinavir, Ritonavir Oral tablet	
<p>Kaletra 100mg-25mg Tablet (00074-0522) (AbbVie US LLC)</p>	 <p>© 2013 GS</p>
<p>Kaletra 200mg-50mg Tablet (00074-6799) (AbbVie US LLC)</p>	 <p>© 2013 GS</p>
<p>Kaletra 200mg-50mg Tablet (55289-0947) (PD-Rx Pharmaceuticals, Inc.)</p>	



Description/Classification

Description

Lopinavir; ritonavir is indicated for use in combination with other antiretroviral medications to treat HIV-1 infections in adults and pediatric patients 14 days and older. Lopinavir is an antiretroviral protease inhibitor. It is formulated with a small amount of ritonavir to increase and maintain adequate lopinavir concentrations. Lopinavir is the active component of the lopinavir; ritonavir formulation.

Updates for coronavirus disease 2019 (COVID-19):

Available data regarding the use of lopinavir; ritonavir in the treatment of COVID-19 due to SARS-CoV-2 are limited and inconclusive. Due to unfavorable pharmacodynamics and negative clinical trial data, the National Institutes of Health (NIH) COVID-19 treatment guidelines recommend against the use of lopinavir; ritonavir outside of clinical trials.^[65314] In a randomized, controlled, open-label trial involving hospitalized patients with confirmed SARS-CoV-2 infection (n = 199), treatment with lopinavir; ritonavir was not associated with a difference from standard of care in the time to clinical improvement and the percentages of patients with detectable viral RNA were similar. In a modified ITT analysis, lopinavir; ritonavir had a median time to clinical improvement that was shorter by 1 day.^[65144] Additional data regarding clinical efficacy for COVID-19 are being evaluated.^[65123] The role of lopinavir; ritonavir in the treatment of COVID-19 is unclear at this time.

Classifications

- [General Anti-infectives Systemic](#)
 - [Antivirals For Systemic Use](#)
 - [HIV Antivirals](#)
 - [Combination HIV Antivirals](#)
 - [Protease Inhibitor Combinations](#)

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References

65123 – World Health Organization (WHO). Coronavirus: landscape analysis of therapeutics as of 17 February 2020. Retrieved March 16, 2020. Available on the World Wide Web at https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1.

65144 – Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. NEJM 2020.

65314 – COVID-19 treatment guidelines panel. COVID-19 treatment guidelines. National Institutes of Health Web site. Accessed April 22, 2020. Available at: <https://covid19treatmentguidelines.nih.gov/>.

Administration Information

General Administration Information

For storage information, see the specific product information within the How Supplied section.

Route-Specific Administration

Oral Administration

Oral Solid Formulations

- *Tablets*: May be taken with or without food. Administered whole; do not crush, break, or chew.[28341]

Oral Liquid Formulations

Oral solution

- Administer with food to enhance absorption.
- Always administer using a calibrated oral dosing syringe or the provided dosing cup. The oral solution is highly concentrated and contains lopinavir 80 mg/ritonavir 20 mg per mL. Pay close attention to dosage of the oral solution, especially in pediatric patients, to ensure appropriate administration and to avoid overdosage.
- The oral solution contains approximately 42% (v/v) alcohol and 15% (w/v) propylene glycol; caution is advised when administering to patients 14 days to 6 months of age. Additionally, the oral solution should be avoided during pregnancy due to the alcohol content.[42452]
- The poor palatability of the oral solution may be difficult to overcome. Options to improve tolerability include numbing the taste buds with ice chips prior to administration, masking the taste by administering with sweet or tangy foods, chocolate syrup, or peanut butter, or flavoring the solution by the pharmacist prior to dispensing.[42452]
- Because the oral solution contains ethanol and propylene glycol, it is not recommended for use with polyurethane feeding tubes due to potential incompatibility. Feeding tubes compatible with ethanol and propylene glycol, such as silicone and polyvinyl chloride (PVC), can be used for administration of lopinavir; ritonavir oral solution. Follow instructions for use of the feeding tube to administer the medication.[28341]

Compounding Drug Information

From Trissel's 2TM Clinical Pharmaceutics Database

Lopinavir and Ritonavir

1. Identity/Properties

Lopinavir has been described as a colorless material and also as a white to light tan powder. Ritonavir is a white to light tan powder having a bitter metallic taste. Solubility: Lopinavir and ritonavir are practically insoluble in water but freely soluble in ethanol and methanol and soluble in isopropanol.

References

Anon. The Merck Index, Whitehouse Station, New Jersey: Merck & Co., Inc. Current edition.

Anon. The United States Pharmacopeia. Rockville, Maryland: The United States Pharmacopeial Convention. Current edition.

Anon. Manufacturer's information and labeling. (Package insert and bulk material data sheet).

2. General Stability Info

The manufacturer of the lopinavir and ritonavir combination (Kaletra) states that the commercial oral tablets should be left in the original packaging or packaged in tight containers. The tablets should be stored at controlled room temperature and protected from exposure to high humidity outside the original container or in an equivalent tight container for more than two weeks is not recommended. The manufacturer also states that the commercial oral liquid formulation should be stored refrigerated at 2 to 8degree C to remain stable until the labeled expiration date. If stored at controlled room temperature, the manufacturer states the oral liquid formulation should be used within two months.

References

Anon. Manufacturer's information and labeling. (Package insert and bulk material data sheet).

3. Enteral Feeds

Prohaska and King reported that the lopinavir and ritonavir combination (Kaletra) has been given by enteral administration via gastrostomy tube, jejunal tube, and percutaneous endoscopic gastronomy tube. King et al. reported that administration of protease inhibitors and non-nucleoside reverse transcriptase inhibitors by a gastrostomy tube to HIV-infected children

provided comparable blood concentrations to oral administration. Leipe et al. published a case report on successfully using a percutaneous endoscopic gastrostomy tube to administer antiretroviral drugs. Kamimura et al. published a case report on successful antiretroviral drugs after gastrojejunal bypass surgery.

References

- Kamimura M, Watanabe K, Kobayakawa M, et al. Successful absorption of retroviral drugs after gastrojejunal bypass surgery following failure of therapy through a jejunal tube. *Intern Med.* 2009; 48:1103-4
- King JR, Yogev R, Aldrovandi G, et al. Pharmacokinetics of antiretrovirals administered to HIV-infected children via gastrostomy tube. *HIV Clin Trials.* 2004; 5:288-93
- Leipe J, Hueber AJ, Rech J, et al. Bypassing non-adherence via PEG in a critically ill HIV-1-infected patient. *AIDS Care.* 2008; 20:863-7
- Prohaska ES, King AR. Administration of antiretroviral medication via enteral tubes. *Am J Health-Syst Pharm.* 2012; 69:2140-6

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References

28341 – Kaletra (lopinavir; ritonavir) tablet and solution package insert. North Chicago, IL: AbbVie Inc; 2020 Mar.

42452 – Panel on Antiretroviral Therapy and Medical Management of HIV-infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Available at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf>. Accessed January 10, 2020.

Adverse Reactions

- abdominal pain
- alopecia
- amenorrhea
- anemia
- angioedema
- anorexia
- anxiety
- appetite stimulation
- arthralgia
- asthenia
- AV block
- back pain
- bleeding
- bradycardia
- breast enlargement
- cardiomyopathy
- cholangitis
- colitis
- constipation
- Cushingoid features
- diabetes mellitus
- diabetic ketoacidosis
- diarrhea
- dizziness
- dysgeusia
- dyspepsia
- elevated hepatic enzymes
- erythema multiforme
- fatigue
- fecal incontinence
- fever
- flatulence
- folliculitis
- furunculosis
- gastritis
- gastroesophageal reflux
- GI bleeding
- gonadal suppression
- gynecomastia
- headache
- hematoma
- hematuria
- hemorrhoids
- hepatitis
- hepatomegaly
- hyperamylasemia
- hyperbilirubinemia
- hypercholesterolemia
- hyperglycemia
- hyperlipidemia
- hyponatremia
- hypophosphatemia
- impotence (erectile dysfunction)
- infection
- insomnia
- jaundice
- lactic acidosis
- leukopenia
- libido decrease
- lipodystrophy
- lymphadenopathy
- maculopapular rash
- menorrhagia
- migraine
- myalgia
- myocardial infarction
- nausea
- neutropenia
- night sweats
- oral ulceration
- osteonecrosis
- pancreatitis
- peptic ulcer
- peripheral neuropathy

- PR prolongation
- pruritus
- QT prolongation
- rash
- renal failure (unspecified)
- rhabdomyolysis
- seborrhea
- seizures
- steatosis
- Stevens-Johnson syndrome
- stomatitis
- thrombocytopenia
- thrombosis
- tinnitus
- torsade de pointes
- toxic epidermal necrolysis
- tremor
- urticaria
- vasculitis
- vertigo
- visual impairment
- vomiting
- weakness
- weight gain
- weight loss
- xerosis
- xerostomia

Adverse events affecting the reproductive system have been reported following use of lopinavir; ritonavir. During clinical trials, less than 2% of lopinavir; ritonavir recipients experienced reproductive adverse events including impotence (erectile dysfunction) (1.7%), libido decrease (0.7%), male gonadal suppression (0.8%), amenorrhea (1.7%), and menorrhagia (1.7%).[\[28341\]](#) [\[51080\]](#)

Pancreatitis, in some cases fatal, has been observed in 1.7% of patients receiving treatment with lopinavir; ritonavir. Marked triglyceride elevations is a risk factor for the development of pancreatitis; marked triglyceride elevations with the development of pancreatitis has occurred with lopinavir; ritonavir. Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence. If clinical symptoms (nausea/vomiting, abdominal pain) or lab abnormalities (hyperamylasemia or increased serum lipase) suggestive of pancreatitis occur, evaluate the patient and hold lopinavir; ritonavir and other antiretroviral therapy as clinically appropriate. In clinical trials with adults, hyperamylasemia (more than 2-times the upper limit of normal) was noted in 3% to 8% of patients. In clinical trials of pediatric patients who received lopinavir; ritonavir oral solution, hyperamylasemia (more than 2.5-times the upper limit of normal) was reported in 7% of patients. In clinical trials with adults, elevated lipase (more than 2-times the upper limit of normal) was reported in 1% to 5% of patients.[\[28341\]](#) [\[51080\]](#)

Gastrointestinal (GI) related disorders were among the most frequently reported adverse events during lopinavir; ritonavir clinical trials, and included diarrhea (19.5% adults; pediatrics 12%), nausea (10.3%), vomiting (6.8% adults; 21% pediatrics), abdominal pain (6.1%), gastroenteritis and colitis (2.5%), and dyspepsia (2%). Other reported GI adverse events include constipation (1%), duodenitis (0.8%), abdominal distension (1.3%), fecal incontinence (0.2%), gastric or peptic ulcer (0.2%), gastritis (0.8%), gastroesophageal reflux disease (1.5%), hemorrhoids (1.5%), flatulence (1.4%), oral ulceration (0.9%), GI bleeding (0.5%), rectal bleeding (0.5%), stomatitis (0.9%), and xerostomia (0.3%).[\[28341\]](#) [\[51080\]](#)

Hyperlipidemia, with large increases in total cholesterol and triglyceride concentrations, has been reported during treatment with lopinavir; ritonavir. In clinical trials in adults, hypercholesterolemia (greater than 300 mg/dL) was reported in 3% to 27% of treatment-naïve patients receiving lopinavir; ritonavir (vs. 5% of control group patients) and in 6% to 39% of treatment-experienced patients (vs. 21% control group). In clinical trials of pediatric patients who received lopinavir; ritonavir oral solution, hypercholesterolemia (greater than 300 mg/dL) was reported in 3% of patients. Also, in adults, hypertriglyceridemia (greater than 750 mg/dL) was reported in 3% to 29% of treatment-naïve patients receiving lopinavir; ritonavir (vs. 1% control group) and in 5% to 36% of treatment-experienced patients (vs. 21% control group). Marked triglyceride elevations is a risk factor for the development of pancreatitis; marked triglyceride elevations with the development of pancreatitis has occurred with lopinavir; ritonavir. Lipid disorders should be managed as clinically appropriate, taking potential drug interactions into account.[\[28341\]](#) [\[51080\]](#)

Elevated hepatic enzymes have been reported during clinical trials of lopinavir; ritonavir, with elevations in SGOT/AST (range: 1% to 10% lopinavir; ritonavir-treated patients vs. 4% to 11% control patients) and SGPT/ALT (range: 1% to 11% vs. 4% to 13%). Hyperbilirubinemia was reported in 1% of adult patients in trials (3% of pediatrics), while elevated GGT was noted in 10% to 29% of adult patients. Hepatitis (3.5%), jaundice, hepatomegaly (0.2%), hepatic steatosis (0.1%), and cholangitis (0.1%) were also reported in patients receiving lopinavir; ritonavir during clinical trials. Patients with underlying hepatitis B or C or marked transaminase elevations prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. There have been postmarketing reports of hepatic dysfunction, including some fatalities, which have generally occurred in patients with advanced HIV disease taking multiple concomitant medications and who have underlying chronic hepatitis or cirrhosis. However, elevated hepatic enzymes (with or without elevated bilirubin), leading to serious hepatic dysfunction in some cases, have been reported in patients without hepatitis.[\[28341\]](#) [\[51080\]](#)

Rash was reported in up to 3.8% of adult patients and 12% of pediatric patients receiving lopinavir; ritonavir during clinical trials. Other dermatologic reactions reported in less than 2% of patients during clinical trials include alopecia (0.4%), dry skin (xerosis), eczema (1.9%), exfoliative dermatitis (1.9%), furunculosis, night sweats (1.6%), pruritus (1.1%), maculopapular rash, and seborrhea (1.9%). Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), and erythema multiforme have been noted in postmarketing reports.[\[28341\]](#) [\[51080\]](#)

Musculoskeletal and generalized adverse reactions reported by recipients of lopinavir; ritonavir during clinical trials included fatigue and asthenia (7.6%), fever, arthralgia and back pain (6.4%), myalgia (1.8%), elevated creatine phosphokinase (more than 4-times upper limits of normal; 4% to 5%), muscle weakness and spasms (1.3%), rhabdomyolysis (0.7%), and osteonecrosis (0.1%).[\[28341\]](#) [\[51080\]](#)

Cardiovascular adverse events reported in patients receiving lopinavir; ritonavir during clinical trials included hypertension (1.8%), deep vein thrombosis (0.7%), myocardial infarction (0.4%), AV block (0.1%), tricuspid valve incompetence (0.1%), capillaritis and vasculitis (0.1%). Bradyarrhythmias (bradycardia), PR prolongation, QT prolongation, and torsade de pointes have been reported in postmarketing surveillance of lopinavir; ritonavir; however, causality has not been established. Lopinavir; ritonavir was evaluated for QT prolongation in a randomized, placebo- and moxifloxacin- (400 mg once-daily) controlled, crossover study in 39 healthy adults; QT intervals were

measured on the third day. Patients received lopinavir; ritonavir at normal doses (400 mg/100 mg twice daily) and supratherapeutic doses (800 mg/200 mg twice daily). The maximum mean (95% upper confidence bound) difference in QT interval in patients versus placebo after baseline correction was 5.3 (8.1) milliseconds in patients receiving normal doses of lopinavir; ritonavir and 15.2 (18.0) milliseconds in patients receiving supratherapeutic doses. Lopinavir; ritonavir 800 mg/200 mg twice daily resulted in a C_{max} that was 2-fold higher than observed with approved once and twice daily regimens at steady state.[\[28341\]](#) [\[51080\]](#)

Dysgeusia was reported in 22% of pediatric patients, and ageusia was noted in 0.7% of adults who received lopinavir; ritonavir during clinical trials.[\[28341\]](#) [\[51080\]](#)

Adverse events affecting the nervous system and special senses reported during lopinavir; ritonavir clinical trials included headache (including migraine, 6.3%), insomnia (3.8%), abnormal dreams (0.7%), anxiety (3.9%), dizziness (1.7%), peripheral neuropathy (2%), cerebral vascular event (0.2%), convulsion or seizures (0.3%), and tremor (0.3%). Visual impairment (0.3%), vertigo (0.3%), and tinnitus (0.2%) have also been reported.[\[28341\]](#) [\[51080\]](#)

In patients receiving lopinavir; ritonavir, neutropenia (less than 750 neutrophils/mm³) was reported in 1% to 5% of adults. Neutrophil counts less than 0.4 x 10⁹/L were reported in 2% of pediatric patients who received lopinavir; ritonavir oral solution in clinical trials. In addition, 4% of pediatric patients who received lopinavir; ritonavir oral solution in clinical trials report thrombocytopenia (platelet counts less than 50,000/mm³). Anemia was noted in 2.1% of adult drug recipients, with 1% to 2% reporting hemoglobin concentrations less than 80 g/L. Leukopenia (1.7%) and lymphadenopathy (1.3%) have also been observed in adults.[\[28341\]](#) [\[51080\]](#)

Increased bleeding, including spontaneous skin hematoma and hemarthrosis, has been reported in HIV infected patients with hemophilia (type A and B) being treated with protease inhibitors. The majority of patients have been able to continue taking their protease inhibitor therapy in spite of bleeding events; some patients received additional coagulation factor. A causal relationship with lopinavir; ritonavir has not been established.[\[28341\]](#) [\[51080\]](#)

A lipodystrophy syndrome (2.2%) consisting of redistribution and accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, gynecomastia, and other cushingoid features have been reported in patients receiving long-term highly active antiretroviral therapy (HAART) that includes protease inhibitors. This syndrome may be associated with metabolic complications such as insulin resistance and dyslipidemia, but not always. The mechanism and long-term consequences are not known. A causal relationship has not been established. Changes in HAART to reverse lipodystrophy should probably be avoided unless the patient finds the changes in body fat intolerable and more conservative interventions fail.[\[28341\]](#) [\[51080\]](#)

Anorexia or decreased appetite (2%) with weight loss (2.3%) was observed in adult patients receiving lopinavir; ritonavir during clinical trials. Other metabolic and nutritional disorders reported in lopinavir; ritonavir recipients included appetite stimulation (0.2%) with weight gain (0.8%) and lactic acidosis (0.4%).[\[28341\]](#) [\[51080\]](#)

In clinical trials, hyperglycemia (glucose more than 250 mg/dL) was observed in 1% to 5% of patients and diabetes mellitus was observed in 1.1% of patients receiving lopinavir; ritonavir in combination with other antiretrovirals. New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with postmarketing use of protease inhibitors. Diabetic ketoacidosis has also occurred. Initiation or adjustment of hypoglycemic therapy is required in some patients after beginning protease inhibitor treatment. In some patients who have discontinued protease inhibitor therapy, hyperglycemia has persisted. However, a causal relationship has not been established. It should also be noted that many of these patients have confounding medical conditions that require therapy with drugs that have been associated with the development of diabetes mellitus or hyperglycemia.[\[28341\]](#) [\[51080\]](#)

In clinical trials of pediatric patients who received lopinavir; ritonavir oral solution, hyponatremia (sodium more than 149 mEq/L) and hyponatremia (less than 130 mEq/L) were reported in 3% of patients each. Additional laboratory abnormalities reported in adults during lopinavir; ritonavir clinical trials include hypophosphatemia (less than 1.5 mg/dL; up to 2%) and hyperuricemia (more than 12 mg/dL; up to 5%).[\[28341\]](#) [\[51080\]](#)

Upper respiratory tract infection (13.9%), lower respiratory tract infection (7.7%), and skin infection (cellulitis and folliculitis; 3.3%) were observed in adults receiving treatment with lopinavir; ritonavir during clinical trials. Viral infections were reported during clinical trials in pediatric patients.[\[28341\]](#) [\[51080\]](#)

Renal and urinary disorders reported in adult patients during lopinavir; ritonavir trials included renal failure (unspecified) (1.2%), hematuria (0.8%), and nephritis (0.1%). Creatinine clearance of less than 50 mL/min was noted in 2% to 3% of adult patients in trials.[\[28341\]](#) [\[51080\]](#)

Adverse events, including death, have resulted from accidental overdose of the lopinavir; ritonavir oral solution in young children. In one case, a 2.1 kg infant experience fatal cardiogenic shock 9 days after receiving a dose 10-fold above the recommended lopinavir dose. Other adverse events occurring in infants receiving unintentional overdoses include bradycardia, complete AV block, cardiomyopathy, lactic acidosis, CNS depression, respiratory complications, and acute renal failure (unspecified). Health care providers are advised to use caution when calculating and administering the oral solution to young children. Further, because the lopinavir; ritonavir solution contains a high concentration of alcohol 42.4% (v/v) and propylene glycol 15.3% (w/v), the manufacturer recommends evaluating all medications being given to the infant to ensure an alcohol and propylene glycol overdose does not occur. If an overdose does occur, administer supportive measures and monitor the patient's vital signs. Gastric lavage and activated charcoal may aid in the removal of unabsorbed drug. The use of dialysis is unlikely to be beneficial as lopinavir is highly protein-bound; however, excess alcohol and propylene glycol may be removed by dialysis.[\[28341\]](#)

Hypersensitivity reactions, including angioedema and urticaria, were reported in 2.7% of patients receiving lopinavir; ritonavir during clinical trials.[\[28341\]](#) [\[51080\]](#)

References

28341 – Kaletra (lopinavir; ritonavir) tablet and solution package insert. North Chicago, IL: AbbVie Inc; 2020 Mar.

51080 – Kaletra (lopinavir; ritonavir) capsule package insert. North Chicago, IL: AbbVie Inc; 2019 Aug.

Contraindications/Precautions

Absolute contraindications are italicized.

- | | |
|--|--|
| <ul style="list-style-type: none">• alcoholism• apheresis• autoimmune disease• AV block• bradycardia• breast-feeding• cardiac disease• cardiomyopathy• celiac disease• children• diabetes mellitus• diabetic ketoacidosis• females• fever• geriatric• Graves' disease• Guillain-Barre syndrome• heart failure• hemophilia• hepatic disease• hepatitis• hepatitis B and HIV coinfection• hepatitis C and HIV coinfection• human immunodeficiency virus (HIV) infection• human immunodeficiency virus (HIV) infection resistance | <ul style="list-style-type: none">• hypercholesterolemia• hyperglycemia• hyperlipidemia• hyperparathyroidism• hypertriglyceridemia• hypocalcemia• hypokalemia• hypomagnesemia• hypothermia• hypothyroidism• immune reconstitution syndrome• infants• jaundice• long QT syndrome• myocardial infarction• neonates• pancreatitis• pheochromocytoma• pregnancy• QT prolongation• rheumatoid arthritis• sickle cell disease• sleep deprivation• stroke• systemic lupus erythematosus (SLE) |
|--|--|
-

Unplanned antiretroviral therapy interruption may be necessary for specific situations, such as serious drug toxicity, intercurrent illness or surgery precluding oral intake, severe hyperemesis gravidarum unresponsive to antiemetics, or drug non-availability. If short-term treatment interruption (i.e., less than 1 to 2 days) is necessary, in general, it is recommended that all antiretroviral agents be discontinued simultaneously, especially if the interruption is because of serious toxicity. However, if a short-term treatment interruption is anticipated in the case of elective surgery, the pharmacokinetic properties and food requirements of specific drugs should be considered. When the antiretroviral regimen contains drugs with differing half-lives, stopping all drugs simultaneously may result in functional monotherapy of the drug with the longest half-life. For example, after discontinuation, the duration of detectable serum concentrations of efavirenz and nevirapine ranges from less than 1 week to more than 3 weeks. Simultaneously stopping all drugs in a regimen containing these agents may result in functional monotherapy with the NNRTI and may increase the risk of NNRTI-resistant mutations. Planned long-term treatment interruptions are not recommended due to the potential for HIV disease progression (i.e., declining CD4 counts, viral rebound, acute viral syndrome), development of minor HIV-associated manifestations or serious non-AIDS complications, development of drug resistance, increased risk of HIV transmission, and increased risk for opportunistic infections. If therapy must be discontinued, counsel the patient on the potential risks and closely monitor for any clinical or laboratory abnormalities.[\[46638\]](#)[\[42452\]](#)

Lopinavir; ritonavir should be used with caution in patients with pre-existing hepatitis. Patients with underlying hepatitis prior to treatment may be at increased risk for developing further enzyme elevations or hepatic decompensation. All patients presenting with HIV infection should be screened for hepatitis B virus (HBV) coinfection to assure appropriate treatment. Patients with hepatitis B and HIV coinfection should be started on a fully suppressive antiretroviral (ARV) regimen with activity against both viruses (regardless of CD4 counts and HBV DNA concentrations). HIV treatment guidelines recommend these patients receive an ARV regimen that contains a dual NRTI backbone of tenofovir alafenamide with emtricitabine or tenofovir disoproxil fumarate with either emtricitabine or lamivudine. If tenofovir cannot be used, entecavir should be used in combination with a fully suppressive ARV regimen (note: entecavir should not be considered part of the ARV regimen). Avoid using single-drug therapy to treat HBV (i.e., lamivudine, emtricitabine, tenofovir, or entecavir as the only active agent) as this may result in HIV resistant strains. Further, HBV treatment regimens that include adefovir or telbivudine should also be avoided, as these regimens are associated with a higher incidence of toxicities and increased rates of HBV treatment failure. Most coinfecting patients should continue treatment indefinitely with the goal of maximal HIV suppression and prevention of HBV relapse. If treatment must be discontinued, monitor transaminase concentrations every 6 weeks for the first 3 months, and every 3 to 6 months thereafter. For patients who refuse a fully suppressive ARV regimen, but still requires treatment for HBV, consider 48 weeks of peginterferon alfa; do not administer HIV-active medications in the absence of a fully suppressive ARV regimen. Instruct coinfecting patients to avoid consuming alcohol, and offer vaccinations against hepatitis A and hepatitis B as appropriate.[\[46638\]](#)[\[28341\]](#) [\[51080\]](#) [\[34362\]](#)

Lopinavir; ritonavir should be used with caution in patients with pre-existing hepatic disease (e.g., alcoholism), liver enzyme abnormalities (e.g., jaundice), or hepatitis. Patients with underlying hepatitis B or C or marked elevations in liver enzymes prior to

treatment may be at increased risk for developing further enzyme elevations or hepatic decompensation. There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis; however, elevated hepatic enzymes (with or without elevated bilirubin), leading to serious hepatic dysfunction in some case, have been reported in patients without underlying hepatitis as early as 7 days after the initiation of lopinavir; ritonavir. Of note, lopinavir; ritonavir was initiated with other antiretrovirals. A causal relationship has not been established. Increased monitoring of LFTs should be considered in these patients, especially during the first several months of treatment.[\[28341\]](#) [\[51080\]](#)

Patients with advanced acquired immunodeficiency syndrome (AIDS) may be at increased risk for developing hypertriglyceridemia and pancreatitis. Patients who exhibit signs or symptoms of pancreatitis (nausea, vomiting, abdominal pain, abnormal serum lipase or amylase concentrations) should discontinue treatment with lopinavir; ritonavir. Fat redistribution and hyperlipidemia have become increasingly recognized side effects with the use of protease inhibitors. Triglyceride and cholesterol testing should be performed prior to beginning lopinavir; ritonavir and at regular intervals during treatment. According to CDC guidelines, patients with hypertriglyceridemia or hypercholesterolemia should be evaluated for risks for cardiovascular events and pancreatitis. If a patient develops hyperlipidemia during treatment with a protease inhibitor, possible interventions include dietary modification, use of lipid lowering agents, or discontinuation of the protease inhibitor. Clinicians should be aware of the potential drug interaction between certain cholesterol-lowering agents and the lopinavir; ritonavir combination.[\[28341\]](#) [\[51080\]](#)

Patients with diabetes mellitus or hyperglycemia may experience an exacerbation of their condition with lopinavir; ritonavir treatment. In some cases, diabetic ketoacidosis has occurred. Further, reports of new-onset diabetes mellitus have been associated with protease inhibitor therapy. Either initiation or dose adjustments of insulin or oral hyperglycemic agents may be required. Drug recipients should be monitored closely for new-onset diabetes mellitus, diabetic ketoacidosis, or hyperglycemia.[\[28341\]](#) [\[51080\]](#)

Protease inhibitors such as lopinavir; ritonavir should be used cautiously in patients with hemophilia A or B due to reports of spontaneous bleeding episodes requiring treatment with additional factor VIII. In many cases, treatment with protease inhibitors was continued or restarted. A causal relationship has not been established.[\[28341\]](#) [\[51080\]](#)

Testing for human immunodeficiency virus (HIV) infection resistance is recommended in all antiretroviral treatment-naïve patients at the time of HIV diagnosis, regardless of whether treatment will be initiated. Additionally, perform resistance testing prior to initiating or changing any HIV treatment regimen.[\[42452\]](#) [\[46638\]](#) Transmission of drug-resistant HIV strains has been both well documented and associated with suboptimal virologic response to initial antiretroviral therapy. In high-income countries (e.g., US, some European countries, Australia, Japan), approximately 10% to 17% of treatment-naïve individuals have resistance mutations to at least 1 antiretroviral drug; up to 8% (but generally less than 5%) of transmitted viruses will exhibit resistance to drugs from more than 1 class. Therefore, resistance testing at baseline can help optimize treatment and, thus, virologic response. In the absence of therapy, resistant viruses may decline over time to less than the detection limit of standard resistance tests, but may still increase the risk of treatment failure when therapy is eventually initiated. Thus, if therapy is deferred, resistance testing should still be performed during acute HIV infection with the genotypic resistance test result kept in the patient's medical record until it becomes clinically useful. Additionally, because of the possibility of acquisition of another drug-resistant virus before treatment initiation, repeat resistance testing at the time therapy is initiated would be prudent. Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of lopinavir; ritonavir following loss of viral suppression may increase the likelihood of antimicrobial resistance to other protease inhibitors.[\[46638\]](#)

Administering lopinavir; ritonavir oral solution to neonates with a postnatal age of less than 14 days or a postmenstrual age (first day of the mother's last menstrual period to birth plus the time since birth) of less than 42 weeks may result in significant alcohol and propylene glycol-related toxicities; use is not recommended. If the benefits of using the oral solution in infants immediately after birth outweighs the potential risk, the manufacturer recommends monitoring for increases in serum osmolality, serum creatinine, and for adverse events such as hyperosmolality, lactic acidosis, renal toxicity, CNS depression (stupor, coma, apnea), seizures, hypotonia, cardiac arrhythmias (ECG changes), and hemolysis. When dosing and administering the oral solution to any pediatric patient, use caution to avoid an overdose. The solution contains approximately 42% (v/v) alcohol and 15% (w/v) propylene glycol; an accidental overdose by a young child could result in significant propylene glycol or alcohol-related toxicities including death. For patients between the ages 14 days and 6 months, health care providers are advised to calculate the total amounts of alcohol and propylene glycol from all medications that are being administered to patient. In children, lopinavir; ritonavir dosages are either based on weight or body surface area (BSA). Typically, a child younger than 12 years will receive less than 5 mL of solution, unless certain enzyme-inducing drugs are prescribed or the child weighs 40 kg or more; the oral solution is highly concentrated and contains lopinavir 80 mg/ritonavir 20 mg per mL. In infants and children 6 months to 12 years of age, the adverse events reported during clinical trials were similar to adults.[\[28341\]](#)

Antiretroviral therapy should be provided to all women during pregnancy, regardless of HIV RNA concentrations or CD4 cell count. Using highly active antiretroviral combination therapy (HAART) to maximally suppress viral replication is the most effective strategy to prevent the development of resistance and to minimize the risk of perinatal transmission. In treatment-naïve women, begin HAART as soon as pregnancy is recognized or HIV is diagnosed, without waiting for the results of resistance testing; subsequent modifications to the treatment regimen should be made once the test results are available. Women who are currently receiving antiretroviral treatment when pregnancy is recognized should continue their treatment regimen if it is currently effective in suppressing viral replication; consider resistance testing if HIV RNA concentrations are more than 500 copies/mL. For women not currently receiving HAART, but who have previously received treatment, obtain a complete and accurate history of all prior antiretroviral regimens used and results of prior resistance testing, and perform resistance testing if HIV RNA concentrations are more than 500 copies/mL; treatment should be initiated prior to receiving resistance test results. Available data from the Antiretroviral Pregnancy Registry, which includes more than 1,400 1st trimester exposures to lopinavir-containing regimens, have shown no difference in the risk of overall major birth defects when compared to the 2.7% background rate among pregnant women in the US. When lopinavir; ritonavir exposures occurred in the 1st trimester, the prevalence of defects was 2.1% (30 out of 1,418 births; 95% CI: 1.4, 3.0). Administer lopinavir; ritonavir twice daily in pregnant patients with no documented lopinavir-associated resistance substitutions; there are insufficient data to recommend dosing for pregnant patients with any documented lopinavir-associated resistance substitutions. Once daily lopinavir; ritonavir dosing is NOT recommended in pregnancy. No dosing adjustment is required for patients during the postpartum period. Avoid use of lopinavir; ritonavir oral solution during pregnancy due to the alcohol content.[\[28341\]](#) [\[47165\]](#) Regular laboratory monitoring is recommended to determine antiretroviral efficacy. Monitor CD4 counts at the initial visit and at least every 3 months during pregnancy; consideration may be given to monitoring

every 6 months in patients on HAART with consistently suppressed viral loads and a CD4 count well above the opportunistic infection threshold. Monitor plasma HIV RNA at the initial visit, 2 to 4 weeks after initiating or changing therapy, monthly until undetectable, then at least every 3 months during pregnancy, and at 34 to 36 weeks gestation. Perform antiretroviral resistance assay (genotypic testing) at baseline in all women with HIV RNA concentrations greater than 500 copies/mL, unless they have already been tested for resistance. First-trimester ultrasound is recommended to confirm gestational age and provide an accurate estimation of gestational age at deliver. A second-trimester ultrasound can be used for both anatomical survey and determination of gestational age in those patients not seen until later in gestation. Perform standard glucose screening in women receiving antiretroviral therapy at 24 to 28 weeks gestation, although it should be noted that some experts would perform earlier screening with ongoing chronic protease inhibitor-based therapy initiated prior to pregnancy, similar to recommendations for women with high-risk factors for glucose intolerance. All pregnant women should be counseled about the importance of adherence to their antiretroviral regimen to reduce the potential for development of resistance and perinatal transmission. It is strongly recommended that antiretroviral therapy, once initiated, not be discontinued. If a woman decides to discontinue therapy, a consultation with an HIV specialist is recommended. It is strongly recommended that health care providers report cases of antenatal antiretroviral drug exposure to the Antiretroviral Pregnancy Registry; telephone 800-258-4263; fax 800-800-1052; the Antiretroviral Pregnancy Registry is also accessible via the Internet.[\[23512\]](#) [\[27468\]](#) [\[28341\]](#)

To reduce the risk of postnatal transmission, HIV-infected mothers within the United States are advised by the Centers for Disease Control and Prevention to avoid breast-feeding. This recommendation applies to both untreated women and women who are receiving antiretroviral therapy. If an HIV-infected mother opts to breast-feed, the infant should undergo immediate diagnostic and virologic HIV testing. Testing should continue throughout breast-feeding and up to 6 months after cessation of breast-feeding. For expert consultation, health care workers may contact the Perinatal HIV Hotline (888-448-8765).[\[42452\]](#) There are limited data regarding lopinavir; ritonavir use of during breast-feeding, and excretion into human breast milk is unknown. In 1 study, breast milk from mothers receiving lopinavir; ritonavir were analyzed with high-performance liquid chromatography and tandem mass spectrometry; the analysis failed to detect either drug in any of the 60 samples. Antiretroviral medications whose passage into human breast milk have been evaluated include nevirapine, zidovudine, lamivudine, and nelfinavir.[\[28341\]](#) [\[46936\]](#) [\[46675\]](#) [\[46679\]](#) [\[46680\]](#) [\[46682\]](#)

Ritonavir prolongs the PR interval in some patients, and postmarketing cases of 2nd- or 3rd-degree AV block have been reported. Lopinavir; ritonavir should be used with caution in patients with cardiac disease such as underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease, and cardiomyopathy, as these patients may be at increased risk for developing cardiac conduction abnormalities. The impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digoxin, and atazanavir) has not been evaluated; however, concomitant administration with such drugs should be undertaken with caution, particularly with those drugs metabolized by cytochrome P450 3A4 isoenzymes. Clinical monitoring is recommended.[\[28315\]](#) [\[51080\]](#)

Cases of QT prolongation and torsade de pointes (TdP) have been reported during postmarketing surveillance. In general, lopinavir; ritonavir should not be used unmonitored in patients with known QT prolongation, with ongoing proarrhythmic conditions that may increase the risk of developing TdP, or receiving drugs that prolong the QT interval.[\[28341\]](#) [\[51080\]](#) Obtain a pre-treatment QTc using a standard 12-lead ECG, telemetry, or mobile ECG device. Obtain baseline electrolytes, including calcium, magnesium, and potassium. Determine if the patient is currently on any QT-prolonging medications that can be discontinued. Document high-risk cardiovascular and comorbid conditions. If the baseline QTc is 500 msec or more and/or the patient has an inherent tendency to develop an exaggerated QTc response (i.e., change of 60 msec or more), correct contributing electrolyte abnormalities, review and discontinue other unnecessary QTc prolonging medications, and proceed with close QTc surveillance. Obtain an initial on-therapy QTc approximately 2 to 4 hours after the first dose and then again at 48 and 96 hours after treatment initiation. If the baseline QTc is 460 to 499 msec (prepubertal), 470 to 499 msec (postpubertal males), or 480 to 499 msec (postpubertal females), correct contributing electrolyte abnormalities, review and discontinue other unnecessary QTc prolonging medications, and obtain an initial on-therapy QTc 48 and 96 hours after treatment initiation. If the baseline QTc is less than 460 msec (prepubertal), less than 470 msec (postpubertal males), or less than 480 msec (postpubertal females), correct electrolyte abnormalities and obtain an initial on-therapy QTc 48 and 96 hours after treatment initiation.[\[65170\]](#) Use lopinavir; ritonavir with caution in patients with conditions that may increase the risk of QT prolongation including congenital long QT syndrome, bradycardia, AV block, heart failure, stress-related cardiomyopathy, myocardial infarction, stroke, hypomagnesemia, hypokalemia, hypocalcemia, or in patients receiving medications known to prolong the QT interval or cause electrolyte imbalances. Females, geriatric patients, patients with sleep deprivation, pheochromocytoma, sickle cell disease, hypothyroidism, hyperparathyroidism, hypothermia, systemic inflammation (e.g., human immunodeficiency virus (HIV) infection, fever, rheumatoid arthritis, systemic lupus erythematosus (SLE), and celiac disease) and patients undergoing apheresis procedures (e.g., plasmapheresis [plasma exchange], cytapheeresis) may also be at increased risk for QT prolongation.[\[28341\]](#) [\[28432\]](#) [\[28457\]](#) [\[56592\]](#) [\[65180\]](#)

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of HIV treatment, patients whose immune system responds to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as progressive multifocal leukoencephalopathy (PML), mycobacterium avium complex (MAC), cytomegalovirus (CMV), Pneumocystis pneumonia, or tuberculosis (TB)), which may necessitate further evaluation and treatment.[\[34362\]](#) In addition, autoimmune disease (including Graves' disease, Guillain-Barre syndrome, and polymyositis) may also develop; the time to onset is variable and may occur months after treatment initiation.[\[28341\]](#)

HIV treatment guidelines recommend all patients presenting with HIV infection undergo testing for hepatitis C, with continued annual screening advised for those persons considered high risk for acquiring hepatitis C. If hepatitis C and HIV coinfection is identified, consider treating both viral infections concurrently. For most patients, the benefits of concurrent therapy outweighs the potential risks (i.e., drug-induced hepatic injury, complex drug interactions, overlapping toxicities); therefore, it is recommended to initiate a fully suppressive antiretroviral (ARV) therapy and a hepatitis C regimen in all coinfecting patients regardless of CD4 count. However, for antiretroviral naive patients with CD4 counts greater than 500 cells/mm³, consideration may be given to deferring ARV until the hepatitis C treatment regimen has been completed. Conversely, for patients with CD4 counts less than 200 cells/mm³, consider delaying initiation of the hepatitis C treatment regimen until the patient is stable on fully suppressive ARV regimen. Instruct coinfecting patients to avoid consuming alcohol, and offer vaccinations against hepatitis A and hepatitis B as appropriate.[\[46638\]](#)

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Mechanism of Action

Lopinavir 400 mg; ritonavir 100 mg given twice daily yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir, with plasma levels of ritonavir less than 7% of those obtained after administration of ritonavir 600 mg twice daily. The in vitro antiviral EC₅₀ (the mean 50% effective concentration) of lopinavir is approximately 10-fold lower than that of ritonavir.

Therefore, the antiviral activity of lopinavir; ritonavir is due to lopinavir. Lopinavir is a competitive inhibitor of HIV protease, an enzyme involved in the replication of HIV. During the later stages of the HIV growth cycle, the gag and gag-pol gene products are first translated into polypeptides and become immature budding particles. Protease is responsible for cleaving these precursor molecules to produce the final structural proteins of a mature virion core and to activate reverse transcriptase for a new round of infection. Thus, protease is necessary for the production of mature virions. Protease inhibition renders the virus noninfectious. Because HIV protease inhibitors

inhibit the HIV replication cycle after translation and before assembly, they are active in acutely and chronically infected cells, and in cells not normally affected by dideoxynucleoside reverse transcriptase inhibitors (i.e., monocytes and macrophages).[28341][53123]

The selection of resistance to lopinavir; ritonavir in treatment-naïve patients has not yet been characterized. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses in vitro. Resistance to lopinavir; ritonavir has been noted in patients who were previously treated with protease inhibitors. In 4 patients with mutations associated with protease inhibitor resistance prior to treatment with lopinavir; ritonavir, additional mutations were noted following viral rebound. Some of these mutations were recognized to be associated with protease inhibitor resistance. In vitro, isolates that displayed greater than 4-fold reduced susceptibility to nelfinavir and saquinavir displayed less than 4-fold reduced susceptibility to lopinavir. Isolates with greater than 4-fold reduced susceptibility to indinavir and ritonavir displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Virologic response to lopinavir; ritonavir is affected by the presence of 3 or more of the following amino acid substitution in protease at baseline: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.[28341]

Lopinavir and ritonavir may bind to M^{Pro}, a key enzyme for coronavirus replication. This may suppress coronavirus activity.[65167]

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Pharmacokinetics

Lopinavir; ritonavir is administered orally. Lopinavir is approximately 98% protein bound to alpha₁-acid glycoprotein and albumin, with a greater affinity for alpha₁-acid glycoprotein. It undergoes oxidative metabolism via the hepatic cytochrome CYP450 system, almost exclusively by the CYP3A isozyme. Ritonavir inhibits CYP3A, thereby increasing plasma concentrations of lopinavir. At least 13 lopinavir oxidative metabolites have been identified in humans. Ritonavir has been shown to induce its own metabolism. Trough lopinavir concentrations decline with time during multiple dosing stabilizing after approximately 10 to 16 days. The half-life of lopinavir is 6.9 +/- 2.2 hours. The majority of lopinavir is excreted as metabolites in the feces (82%), with about 10% of the dose appearing in the urine.[28341][51080]

Affected cytochrome P450 isoenzymes and drug transporters: CYP3A4, CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2B6, Organic Anion Transporting Polypeptide 1B1 (OATP1B1), P-glycoprotein (P-gp), glucuronosyl transferase (UGT)

When given as single agents, lopinavir is a substrate of CYP3A4 and an inhibitor of the drug transporter OATP1B1.[28341][56579] Ritonavir is a substrate, inducer, and potent inhibitor of CYP3A4 (in vivo and in vitro), a partial substrate and minor inhibitor of CYP2D6, and a substrate and inhibitor of P-gp. Ritonavir also appears to induce CYP1A2 and UGT. According to the manufacturer, ritonavir may induce CYP2C9, CYP2C19, and CYP2B6. Ritonavir has been associated with many clinically significant drug interactions; however, the magnitude and effect of ritonavir on the pharmacokinetics of coadministered drugs are difficult to predict due to various CYP enzymes that are affected and the potential of ritonavir to induce or inhibit these enzymes. Interactions with drugs that are substrates of multiple CYP enzymes or that have a low intrinsic CYP3A clearance are especially difficult to predict. Drugs metabolized by CYP3A4 are expected to have large (greater than 3-fold) increases in the AUC when coadministered with ritonavir; drugs metabolized by CYP2D6 may display up to a 2-fold increase in AUC when coadministered with treatment doses of ritonavir. However, according to the manufacturer of lopinavir; ritonavir, the booster dose of ritonavir used in the combination product is unlikely to cause inhibition of CYP2D6.[26120][27493][28315][28341][28380][34557][47165]

Route-Specific Pharmacokinetics

• Oral Route

Lopinavir; ritonavir tablets were compared to the original capsule formulation, which is no longer available. Similar lopinavir and ritonavir plasma concentrations are seen following the administration of 2 lopinavir; ritonavir tablets (200 mg; 50 mg each) compared to lopinavir; ritonavir capsules (133.3 mg; 33.3 mg each) under fed conditions; however, less pharmacokinetic variability was seen following the administration of the tablets. In HIV-infected patients, 400 mg/100 mg lopinavir; ritonavir administered twice daily yields the mean lopinavir C_{max} of 9.8 +/- 3.7 mcg/mL approximately 4 hours after administration. In comparison, once-daily dosing of 800 mg/200 mg yields the mean lopinavir C_{max} of 11.8 +/- 3.7 mcg/mL. The lopinavir AUC

over a 24-hour dosing interval is approximately 1.5-times that seen with a 12-hour dosing interval (154.1 +/- 61.4 mcg x h/mL vs. 92.6 +/- 36.7 mcg x h/mL, respectively). Also, once-daily administration of lopinavir; ritonavir yields trough concentrations that are approximately 60% of the concentrations achieved after twice-daily administration (1.7 +/- 1.6 mcg/mL vs. 5.5 +/- 2.7 mcg/mL respectively).[28341]

Relative to fasting, the administration of lopinavir; ritonavir oral solution with a meal increases lopinavir AUC by 130%. To enhance bioavailability and minimize pharmacokinetic variability, lopinavir; ritonavir oral solution should be administered with food. Relative to fasting, administration of lopinavir; ritonavir tablets with a meal increases lopinavir AUC by 19%. These pharmacokinetic alterations were not found to be clinically relevant, and lopinavir; ritonavir tablets may be taken with or without food.[28341]

Special Populations

• Hepatic Impairment

Lopinavir is extensively metabolized by the liver; hepatic dysfunction alters the pharmacokinetic parameters of lopinavir; ritonavir. In 1 small study, multiple doses of 400 mg/100 mg lopinavir; ritonavir were given twice daily to HIV and HCV coinfecting patients with mild to moderate hepatic impairment (n = 12). An evaluation of the data found the AUC and C_{max} of lopinavir to be increased by 30% and 20%, respectively, compared to HIV-infected patients with normal hepatic function (n = 12). Additionally, the plasma protein binding of lopinavir was significantly lower in both mild and moderate hepatic impairment compared to controls (99.09% vs. 99.31%, respectively). Lopinavir; ritonavir has not been studied in patients with severe hepatic impairment.[28341]

• Renal Impairment

Pharmacokinetics of lopinavir; ritonavir are not altered in patients with renal dysfunction. Lopinavir pharmacokinetics have not been studied in patients with renal impairment, although no change in total clearance of lopinavir is expected in patients with renal dysfunction.[28341]

• Pediatrics

Infants 6 to 11 months, Children, and Adolescents

The clearance of lopinavir; ritonavir is higher in younger children and decreases with increasing age.[53197] Children have a lower drug exposure of lopinavir; ritonavir compared with adults when treated with doses that are directly scaled for body surface areas (BSA). The directly scaled dose of 230 mg/57.5 mg/m² of lopinavir; ritonavir would be comparable to the adult dose of 400 mg/100 mg; however, younger children have increased lopinavir clearance and higher doses of the drug would be needed to achieve drug exposures similar to adults with standard dosing. The pediatric dose needs to be increased by 30% to achieve similar trough concentrations compared to those observed in adults.[42452] In a study of pediatric patients ranging in age from 6 months to 12 years, the mean lopinavir trough concentration was 4.74 +/- 2.93 mcg/mL for doses of 230 mg/57.4 mg/m² (n = 12), while the mean trough concentration was 7.91 +/- 4.52 mcg/mL for doses of 300 mg/75 mg/m² (n = 15) compared to the adult value of 7.1 +/- 4.52 mcg/mL.[28341][42452][53193] In a study of 23 children, aged 4.8 months to 13 years treated with lopinavir; ritonavir 230 mg/57.5 mg/m², the mean AUC and C_{min} were lower than those observed in adults treated with doses of 400 mg/100 mg. Additionally, a C_{min} of less than 1 mg/L was noted in 7 patients (5 patients younger than 2 years and 2 patients older than 2 years, p = 0.011). Lower age was significantly correlated with a lower C_{min} (p = 0.003) and AUC (p = 0.009).[42452][53194] The mean half-life reported in studies was 5.8 to 7.6 hours.[53193][53194]

Neonates and Infants 1 to 5 months

The clearance of lopinavir; ritonavir is dependent on weight and postmenstrual age in neonates and infants and decreases with increasing age.[53195][53197] The pharmacokinetics of the oral solution at a dose of approximately 300 mg/75 mg/m² twice daily have been evaluated in infants 14 days and older to younger than 6 weeks of age (n = 9) and between 6 weeks and 6 months of age (n = 18). The mean steady-state lopinavir AUC, C_{max}, and trough were 43.4 +/- 14.8 mcg x hour/mL, 5.2 +/- 1.8 mcg/mL, and 2.5 mcg/mL, respectively, in neonates and infants 14 days and older and younger than 6 weeks of age. The mean half-life was 3.67 +/- 1.46 hours. The mean lopinavir AUC, C_{max}, and trough were 74.5 +/- 37.9 mcg x hour/mL, 9.4 +/- 4.9 mcg/mL, and 2.7 mcg/mL, respectively, in infants between 6 weeks and 6 months of age. The mean half-life was 4.24 +/- 2.83 hours.[28341][42452][53195][53196]

• Other

Pregnancy

Administration of standard dose of lopinavir; ritonavir to women during the second and third trimesters of pregnancy results in reduced systemic drug exposure (AUC). In 1 study involving 17 HIV-infected pregnant women in their third trimester, standard lopinavir; ritonavir dosing resulted in AUC values that were 46% lower than those observed in the nonpregnant control group. Another study, a population pharmacokinetic model, found systemic clearance of lopinavir increased by 38% early in the second trimester. Based on these data, HIV guidelines suggest the use of higher doses (i.e., 600 mg lopinavir; 150 mg ritonavir) given twice daily during the second and third trimesters. If standard dosing is used, closely monitor virologic

response and lopinavir drug concentrations (if available). Avoid use of the once-daily dosing regimen throughout pregnancy as no pharmacokinetic data are available. Lopinavir; ritonavir has low placental transfer to the fetus.[23512] [60126]

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Pregnancy/Breast-feeding

Pregnancy

Antiretroviral therapy should be provided to all women during pregnancy, regardless of HIV RNA concentrations or CD4 cell count. Using highly active antiretroviral combination therapy (HAART) to maximally suppress viral replication is the most effective strategy to prevent the development of resistance and to minimize the risk of perinatal transmission. In treatment-naïve women, begin HAART as soon as pregnancy is recognized or HIV is diagnosed, without waiting for the results of resistance testing; subsequent modifications to the treatment regimen should be made once the test results are available. Women who are currently receiving antiretroviral treatment when pregnancy is recognized should continue their treatment regimen if it is currently effective in suppressing viral replication; consider resistance testing if HIV RNA concentrations are more than 500 copies/mL. For women not currently receiving HAART, but who have previously received treatment, obtain a complete and accurate history of all prior antiretroviral regimens used and results of prior resistance testing, and perform resistance testing if HIV RNA concentrations are more than 500 copies/mL; treatment should be initiated prior to receiving resistance test results. Available data from the Antiretroviral Pregnancy Registry, which includes more than 1,400 1st trimester exposures to lopinavir-containing regimens, have shown no difference in the risk of overall major birth defects when compared

to the 2.7% background rate among pregnant women in the US. When lopinavir; ritonavir exposures occurred in the 1st trimester, the prevalence of defects was 2.1% (30 out of 1,418 births; 95% CI: 1.4, 3.0). Administer lopinavir; ritonavir twice daily in pregnant patients with no documented lopinavir-associated resistance substitutions; there are insufficient data to recommend dosing for pregnant patients with any documented lopinavir-associated resistance substitutions. Once daily lopinavir; ritonavir dosing is NOT recommended in pregnancy. No dosing adjustment is required for patients during the postpartum period. Avoid use of lopinavir; ritonavir oral solution during pregnancy due to the alcohol content.[28341] [47165] Regular laboratory monitoring is recommended to determine antiretroviral efficacy. Monitor CD4 counts at the initial visit and at least every 3 months during pregnancy; consideration may be given to monitoring every 6 months in patients on HAART with consistently suppressed viral loads and a CD4 count well above the opportunistic infection threshold. Monitor plasma HIV RNA at the initial visit, 2 to 4 weeks after initiating or changing therapy, monthly until undetectable, then at least every 3 months during pregnancy, and at 34 to 36 weeks gestation. Perform antiretroviral resistance assay (genotypic testing) at baseline in all women with HIV RNA concentrations greater than 500 copies/mL, unless they have already been tested for resistance. First-trimester ultrasound is recommended to confirm gestational age and provide an accurate estimation of gestational age at deliver. A second-trimester ultrasound can be used for both anatomical survey and determination of gestational age in those patients not seen until later in gestation. Perform standard glucose screening in women receiving antiretroviral therapy at 24 to 28 weeks gestation, although it should be noted that some experts would perform earlier screening with ongoing chronic protease inhibitor-based therapy initiated prior to pregnancy, similar to recommendations for women with high-risk factors for glucose intolerance. All pregnant women should be counseled about the importance of adherence to their antiretroviral regimen to reduce the potential for development of resistance and perinatal transmission. It is strongly recommended that antiretroviral therapy, once initiated, not be discontinued. If a woman decides to discontinue therapy, a consultation with an HIV specialist is recommended. It is strongly recommended that health care providers report cases of antenatal antiretroviral drug exposure to the Antiretroviral Pregnancy Registry; telephone 800-258-4263; fax 800-800-1052; the Antiretroviral Pregnancy Registry is also accessible via the Internet.[23512] [27468] [28341]

Breast-Feeding

To reduce the risk of postnatal transmission, HIV-infected mothers within the United States are advised by the Centers for Disease Control and Prevention to avoid breast-feeding. This recommendation applies to both untreated women and women who are receiving antiretroviral therapy. If an HIV-infected mother opts to breast-feed, the infant should undergo immediate diagnostic and virologic HIV testing. Testing should continue throughout breast-feeding and up to 6 months after cessation of breast-feeding. For expert consultation, health care workers may contact the Perinatal HIV Hotline (888-448-8765).[42452] There are limited data regarding lopinavir; ritonavir use of during breast-feeding, and excretion into human breast milk is unknown. In 1 study, breast milk from mothers receiving lopinavir; ritonavir were analyzed with high-performance liquid chromatography and tandem mass spectrometry; the analysis failed to detect either drug in any of the 60 samples. Antiretroviral medications whose passage into human breast milk have been evaluated include nevirapine, zidovudine, lamivudine, and nelfinavir.[28341] [46936] [46675] [46679] [46680] [46682]

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Interactions

Level 1 (Severe)

- Alfuzosin
- Apalutamide
- Atazanavir; Cobicistat
- Belladonna Alkaloids; Ergotamine; Phenobarbital
- Bepridil
- Caffeine; Ergotamine
- Cisapride
- Cobicistat
- Conivaptan
- Darunavir; Cobicistat
- Darunavir; Cobicistat; Emtricitabine; Tenofovir alafenamide
- Dihydroergotamine
- Dronedarone
- Elbasvir; Grazoprevir
- Eletriptan
- Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Alafenamide
- Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Disoproxil Fumarate
- Enzalutamide
- Eplerenone
- Ergoloid Mesylates
- Ergonovine
- Ergot alkaloids
- Ergotamine
- Ezetimibe; Simvastatin
- Flibanserin
- Idelalisib
- Isavuconazonium
- Isoniazid, INH; Pyrazinamide, PZA; Rifampin
- Isoniazid, INH; Rifampin
- Ivabradine
- Lomitapide
- Lovastatin
- Lovastatin; Niacin
- Lurasidone
- Meperidine
- Meperidine; Promethazine
- Methylergonovine
- Methysergide
- Mitotane
- Naloxegol
- Niacin; Simvastatin
- Pergolide
- Pimozide
- Ranolazine
- Red Yeast Rice
- Rifampin
- Silodosin
- Simvastatin
- Simvastatin; Sitagliptin
- St. John's Wort, Hypericum perforatum
- Terfenadine
- Thioridazine
- Tolvaptan
- Triazolam
- Ubrogepant

Level 2 (Major)

- Abemaciclib
- Acalabrutinib
- Acetaminophen; Butalbital
- Acetaminophen; Butalbital; Caffeine
- Acetaminophen; Butalbital; Caffeine; Codeine
- Acetaminophen; Tramadol
- Acridinium; Formoterol
- Adefovir
- Ado-Trastuzumab emtansine
- Albuterol
- Albuterol; Ipratropium
- Almotriptan
- Alosetron
- Alprazolam
- Amiodarone
- Amitriptyline; Chlordiazepoxide
- Amlodipine; Atorvastatin
- Amobarbital
- Amoxapine
- Amoxicillin; Clarithromycin; Lansoprazole
- Amoxicillin; Clarithromycin; Omeprazole
- Anagrelide
- Apixaban
- Apomorphine
- Aprepitant, Fosaprepitant
- Arformoterol
- Aripiprazole
- Armodafinil
- Arsenic Trioxide
- Artemether; Lumefantrine
- Asenapine
- Aspirin, ASA; Butalbital; Caffeine
- Aspirin, ASA; Butalbital; Caffeine; Codeine
- Atomoxetine
- Atorvastatin
- Atorvastatin; Ezetimibe
- Atropine; Hyoscyamine; Phenobarbital; Scopolamine
- Avanafil
- Avapritinib
- Avatrombopag
- Axitinib
- Azelastine; Fluticasone
- Azithromycin
- Barbiturates
- Bedaquiline
- Betrixaban
- Bexarotene
- Bicalutamide
- Bismuth Subcitrate Potassium; Metronidazole; Tetracycline
- Bismuth Subsalicylate; Metronidazole; Tetracycline
- Boceprevir
- Bosentan
- Bosutinib
- Brexpiprazole
- Brigatinib
- Bromocriptine
- Budesonide
- Budesonide; Formoterol
- Buprenorphine
- Buprenorphine; Naloxone
- Buspirone
- Butabarbital
- Cabazitaxel
- Cabozantinib

- Carbamazepine
- Cariprazine
- Ceritinib
- Cevimeline
- Chlordiazepoxide
- Chlordiazepoxide; Clidinium
- Chloroquine
- Chlorpromazine
- Cilostazol
- Ciprofloxacin
- Citalopram
- Clarithromycin
- Clofazimine
- Clopidogrel
- Clorazepate
- Clozapine
- Cobimetinib
- Codeine; Phenylephrine; Promethazine
- Codeine; Promethazine
- Colchicine
- Colchicine; Probenecid
- Conjugated Estrogens; Medroxyprogesterone
- Copanlisib
- Crizotinib
- Cyclosporine
- Dabrafenib
- Daclatasvir
- Dapagliflozin; Saxagliptin
- Darunavir
- Dasabuvir; Ombitasvir; Paritaprevir; Ritonavir
- Dasatinib
- Deferasirox
- Deflazacort
- Degarelix
- Deutetrabenazine
- Dexamethasone
- Dextromethorphan; Promethazine
- Dextromethorphan; Quinidine
- Diazepam
- Digoxin
- Diltiazem
- Disopyramide
- Disulfiram
- Docetaxel
- Dofetilide
- Dolasetron
- Dolutegravir; Rilpivirine
- Donepezil
- Donepezil; Memantine
- Doxorubicin
- Doxorubicin Liposomal
- Dronabinol
- Droperidol
- Drospirenone; Ethinyl Estradiol
- Drospirenone; Ethinyl Estradiol; Levomefolate
- Dutasteride; Tamsulosin
- Duvelisib
- Efavirenz
- Efavirenz; Emtricitabine; Tenofovir
- Efavirenz; Lamivudine; Tenofovir Disoproxil Fumarate
- Elagolix
- Elexacaftor; tezacaftor; ivacaftor
- Eliglustat
- Eluxadoline
- Emtricitabine; Rilpivirine; Tenofovir alafenamide
- Emtricitabine; Rilpivirine; Tenofovir disoproxil fumarate
- Encainide
- Encorafenib
- Entrectinib
- Erdafitinib
- Eribulin
- Erlotinib
- Erythromycin
- Erythromycin; Sulfisoxazole
- Escitalopram
- Eslicarbazepine
- Estradiol Cypionate; Medroxyprogesterone
- Estradiol; Levonorgestrel
- Eszopiclone
- Ethanol
- Ethinyl Estradiol
- Ethinyl Estradiol; Desogestrel
- Ethinyl Estradiol; Ethynodiol Diacetate
- Ethinyl Estradiol; Etonogestrel
- Ethinyl Estradiol; Levonorgestrel
- Ethinyl Estradiol; Levonorgestrel; Ferrous bisglycinate
- Ethinyl Estradiol; Levonorgestrel; Folic Acid; Levomefolate
- Ethinyl Estradiol; Norelgestromin
- Ethinyl Estradiol; Norethindrone
- Ethinyl Estradiol; Norethindrone Acetate
- Ethinyl Estradiol; Norethindrone Acetate; Ferrous fumarate
- Ethinyl Estradiol; Norethindrone; Ferrous fumarate
- Ethinyl Estradiol; Norgestimate
- Ethinyl Estradiol; Norgestrel
- Ethotoin
- Etonogestrel
- Everolimus
- Ezogabine
- Fedratinib
- Felbamate
- Fentanyl
- Fingolimod
- Flecainide
- Fluconazole
- Fluoxetine
- Fluoxetine; Olanzapine
- Fluphenazine
- Flurazepam
- Fluticasone
- Fluticasone; Salmeterol
- Fluticasone; Umeclidinium; Vilanterol
- Fluticasone; Vilanterol
- Fluvoxamine
- Formoterol
- Formoterol; Mometasone
- Fosamprenavir
- Foscarnet
- Fosphenytoin
- Gemifloxacin
- Gemtuzumab Ozogamicin
- Gilteritinib
- Glasdegib
- Glecaprevir; Pibrentasvir
- Glycopyrrolate; Formoterol
- Goserelin
- Granisetron
- Guanfacine
- Halogenated Anesthetics
- Haloperidol
- Histrelin
- Hydantoins
- Hydroxychloroquine
- Hydroxyzine
- Ibrutinib
- Ibutilide
- Iloperidone
- Imatinib
- Indacaterol
- Indacaterol; Glycopyrrolate
- Inotuzumab Ozogamicin
- Interferon Alfa-2b; Ribavirin
- Irinotecan
- Irinotecan Liposomal
- Istradefylline
- Itraconazole

- Ivacaftor
- Ivosidenib
- Ixabepilone
- Ketoconazole
- Lamotrigine
- Lanthanum Carbonate
- Lapatinib
- Larotrectinib
- Lefamulin
- Lemborexant
- Lenvatinib
- Leuprolide
- Leuprolide; Norethindrone
- Levalbuterol
- Levofloxacin
- Levomethadyl
- Levomilnacipran
- Levonorgestrel
- Lithium
- Lofexidine
- Long-acting beta-agonists
- Loperamide
- Loperamide; Simethicone
- Lorlatinib
- Lumacaftor; Ivacaftor
- Lumacaftor; Ivacaftor
- Lumateperone
- Macimorelin
- Macitentan
- Maprotiline
- Maraviroc
- Medroxyprogesterone
- Mefloquine
- Mephobarbital
- Mesoridazine
- Mestranol; Norethindrone
- Metaproterenol
- Metformin; Saxagliptin
- Methadone
- Methohexital
- Metronidazole
- Mexiletine
- Midazolam
- Midostaurin
- Mifepristone
- Mirtazapine
- Modafinil
- Moxifloxacin
- Nafcillin
- Naldemedine
- Nefazodone
- Nelfinavir
- Neratinib
- Netupitant, Fosnetupitant; Palonosetron
- Nevirapine
- Nifedipine
- Nilotinib
- Norfloxacin
- Octreotide
- Ofloxacin
- Olanzapine
- Olaparib
- Olodaterol
- Ombitasvir; Paritaprevir; Ritonavir
- Omeprazole; Amoxicillin; Rifabutin
- Ondansetron
- Oritavancin
- Orlistat
- Osilodrostat
- Osimertinib
- Ospemifene
- Oxaliplatin
- Oxcarbazepine
- Palbociclib
- Paliperidone
- Panobinostat
- Paroxetine
- Pasireotide
- Pazopanib
- Pentamidine
- Pentobarbital
- Perphenazine
- Perphenazine; Amitriptyline
- Pexidartinib
- Phenobarbital
- Phenylephrine; Promethazine
- Phenytoin
- Pimavanserin
- Pirbuterol
- Pitolisant
- Ponatinib
- Posaconazole
- Primaquine
- Primidone
- Procainamide
- Prochlorperazine
- Promethazine
- Propafenone
- Quazepam
- Quetiapine
- Quinidine
- Quinine
- Regorafenib
- Revefenacin
- Ribavirin
- Ribociclib
- Ribociclib; Letrozole
- Rifabutin
- Rifapentine
- Rilpivirine
- Rimegepant
- Riociguat
- Risperidone
- Rivaroxaban
- Roflumilast
- Romidepsin
- Rosuvastatin
- Ruxolitinib
- Salmeterol
- Saquinavir
- Saxagliptin
- Secobarbital
- Segesterone Acetate; Ethinyl Estradiol
- Selumetinib
- Sertraline
- Short-acting beta-agonists
- Sildenafil
- Simeprevir
- Siponimod
- Sirolimus
- Sodium Oxybate
- Sofosbuvir; Velpatasvir; Voxilaprevir
- Solifenacin
- Sonidegib
- Sorafenib
- Sotalol
- Sunitinib
- Suvorexant
- Tacrolimus
- Tadalafil
- Tamoxifen
- Tamsulosin
- Tasimelteon
- Tazemetostat
- Telaprevir
- Telavancin

- Telithromycin
- Temsirolimus
- Terbutaline
- Tetrabenazine
- Tezacaftor; Ivacaftor
- Thiopental
- Thiotepa
- Ticagrelor
- Tiotropium; Olodaterol
- Tofacitinib
- Tolterodine
- Topotecan
- Toremifene
- Trabectedin
- Tramadol
- Trazodone
- Tricyclic antidepressants
- Trifluoperazine
- Triptorelin
- Umeclidinium; Vilanterol

- Valbenazine
- Valproic Acid, Divalproex Sodium
- Vandetanib
- Vardenafil
- Vemurafenib
- Venetoclax
- Venlafaxine
- Vilazodone
- Vinblastine
- Vincristine
- Vincristine Liposomal
- Vorapaxar
- Voriconazole
- Vorinostat
- Voxelotor
- Warfarin
- Zalcitabine, ddC
- Zanubrutinib
- Ziprasidone

Level 3 (Moderate)

- Acarbose
- Acebutolol
- Acetaminophen
- Acetaminophen; Aspirin, ASA; Caffeine
- Acetaminophen; Caffeine
- Acetaminophen; Caffeine; Dihydrocodeine
- Acetaminophen; Caffeine; Magnesium Salicylate; Phenyltoloxamine
- Acetaminophen; Caffeine; Phenyltoloxamine; Salicylamide
- Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine
- Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine
- Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine
- Acetaminophen; Codeine
- Acetaminophen; Dextromethorphan
- Acetaminophen; Dextromethorphan; Doxylamine
- Acetaminophen; Dextromethorphan; Guaifenesin; Phenylephrine
- Acetaminophen; Dextromethorphan; Phenylephrine
- Acetaminophen; Dextromethorphan; Pseudoephedrine
- Acetaminophen; Dichloralphenazone; Isometheptene
- Acetaminophen; Diphenhydramine
- Acetaminophen; Guaifenesin; Phenylephrine
- Acetaminophen; Hydrocodone
- Acetaminophen; Oxycodone
- Acetaminophen; Pentazocine
- Acetaminophen; Propoxyphene
- Acetaminophen; Pseudoephedrine
- Afatinib
- Aldesleukin, IL-2
- Alfentanil
- Aliskiren
- Aliskiren; Amlodipine
- Aliskiren; Amlodipine; Hydrochlorothiazide, HCTZ
- Aliskiren; Hydrochlorothiazide, HCTZ
- Aliskiren; Valsartan
- Alogliptin
- Alogliptin; Metformin
- Alogliptin; Pioglitazone
- Alpha-glucosidase Inhibitors
- Amitriptyline
- Amlodipine
- Amlodipine; Benazepril
- Amlodipine; Celecoxib
- Amlodipine; Hydrochlorothiazide, HCTZ; Olmesartan
- Amlodipine; Hydrochlorothiazide, HCTZ; Valsartan
- Amlodipine; Olmesartan
- Amlodipine; Telmisartan

- Amlodipine; Valsartan
- Amphetamine
- Amphetamine; Dextroamphetamine
- Amphetamines
- Aspirin, ASA; Caffeine; Dihydrocodeine
- Aspirin, ASA; Carisoprodol; Codeine
- Aspirin, ASA; Citric Acid; Sodium Bicarbonate
- Aspirin, ASA; Omeprazole
- Aspirin, ASA; Oxycodone
- Atenolol
- Atenolol; Chlorthalidone
- Belladonna; Opium
- Bendroflumethiazide; Nadolol
- Benzhydrocodone; Acetaminophen
- Benzphetamine
- Betamethasone
- Betaxolol
- Bictegravir; Emtricitabine; Tenofovir Alafenamide
- Bisoprolol
- Bisoprolol; Hydrochlorothiazide, HCTZ
- Bortezomib
- Brimonidine; Timolol
- Brompheniramine; Guaifenesin; Hydrocodone
- Brompheniramine; Hydrocodone; Pseudoephedrine
- Bupivacaine; Lidocaine
- Bupropion
- Bupropion; Naltrexone
- Calcifediol
- Canagliflozin
- Canagliflozin; Metformin
- Cannabidiol
- Carbetapentane; Chlorpheniramine
- Carbetapentane; Chlorpheniramine; Phenylephrine
- Carbetapentane; Diphenhydramine; Phenylephrine
- Carbinoxamine; Hydrocodone; Phenylephrine
- Carbinoxamine; Hydrocodone; Pseudoephedrine
- Carteolol
- Carvedilol
- Cetirizine
- Cetirizine; Pseudoephedrine
- Chloramphenicol
- Chlorpheniramine
- Chlorpheniramine; Codeine
- Chlorpheniramine; Dextromethorphan
- Chlorpheniramine; Dextromethorphan; Phenylephrine
- Chlorpheniramine; Dihydrocodeine; Phenylephrine
- Chlorpheniramine; Dihydrocodeine; Pseudoephedrine
- Chlorpheniramine; Guaifenesin; Hydrocodone; Pseudoephedrine
- Chlorpheniramine; Hydrocodone

- Chlorpheniramine; Hydrocodone; Phenylephrine
- Chlorpheniramine; Hydrocodone; Pseudoephedrine
- Chlorpheniramine; Phenylephrine
- Chlorpheniramine; Pseudoephedrine
- Ciclesonide
- Cidofovir
- Cimetidine
- Cinacalcet
- Clevidipine
- Clindamycin
- Clobazam
- Clofarabine
- Clomipramine
- Clonazepam
- Cocaine
- Codeine
- Codeine; Guaifenesin
- Conjugated Estrogens
- Conjugated Estrogens; Bazedoxifene
- Cyclophosphamide
- Dabigatran
- Dapagliflozin
- Dapagliflozin; Metformin
- Dapsone
- Darifenacin
- Darolutamide
- Delavirdine
- Desipramine
- Dexlansoprazole
- Dexmedetomidine
- Dextroamphetamine
- Dextromethorphan; Diphenhydramine; Phenylephrine
- Diclofenac
- Diclofenac; Misoprostol
- Dienogest; Estradiol valerate
- Dihydrocodeine; Guaifenesin; Pseudoephedrine
- Diphenhydramine
- Diphenhydramine; Hydrocodone; Phenylephrine
- Diphenhydramine; Ibuprofen
- Diphenhydramine; Naproxen
- Diphenhydramine; Phenylephrine
- Doravirine; Lamivudine; Tenofovir disoproxil fumarate
- Dorzolamide; Timolol
- Doxazosin
- Doxepin
- Doxercalciferol
- Drospirenone; Estradiol
- Dutasteride
- Echinacea
- Edoxaban
- Eltrombopag
- Elvitegravir
- Empagliflozin
- Empagliflozin; Linagliptin
- Empagliflozin; Linagliptin; Metformin
- Empagliflozin; Metformin
- Emtricitabine; Tenofovir alafenamide
- Emtricitabine; Tenofovir disoproxil fumarate
- Enalapril; Felodipine
- Enfortumab vedotin
- Ertugliflozin; Metformin
- Esmolol
- Esomeprazole
- Esomeprazole; Naproxen
- Estazolam
- Esterified Estrogens
- Esterified Estrogens; Methyltestosterone
- Estradiol
- Estradiol; Norethindrone
- Estradiol; Norgestimate
- Estradiol; Progesterone
- Estropipate
- Ethosuximide

- Etravirine
- Felodipine
- Fesoterodine
- Fluvastatin
- food
- Fostamatinib
- Galantamine
- Gefitinib
- Glipizide; Metformin
- Glyburide; Metformin
- grapefruit juice
- Guaifenesin; Hydrocodone
- Guaifenesin; Hydrocodone; Pseudoephedrine
- Halofantrine
- Homatropine; Hydrocodone
- Hydrochlorothiazide, HCTZ; Losartan
- Hydrochlorothiazide, HCTZ; Metoprolol
- Hydrochlorothiazide, HCTZ; Propranolol
- Hydrochlorothiazide, HCTZ; Valsartan
- Hydrocodone
- Hydrocodone; Ibuprofen
- Hydrocodone; Phenylephrine
- Hydrocodone; Potassium Guaiacolsulfonate
- Hydrocodone; Potassium Guaiacolsulfonate; Pseudoephedrine
- Hydrocodone; Pseudoephedrine
- Hydroxyprogesterone
- Ibuprofen; Oxycodone
- Ifosfamide
- Imipramine
- Incretin Mimetics
- Insulins
- Interferons
- Isradipine
- Ketamine
- Labetalol
- Lacosamide
- Lamivudine; Tenofovir Disoproxil Fumarate
- Lansoprazole
- Lansoprazole; Naproxen
- Ledipasvir; Sofosbuvir
- Lesinurad
- Lesinurad; Allopurinol
- Letermovir
- Levocetirizine
- Levorphanol
- Lidocaine
- Linagliptin
- Linagliptin; Metformin
- Lisdexamfetamine
- Losartan
- Meclizine
- Meloxicam
- Metformin
- Metformin; Pioglitazone
- Metformin; Repaglinide
- Metformin; Rosiglitazone
- Metformin; Sitagliptin
- Methamphetamine
- Methylprednisolone
- Metoclopramide
- Metoprolol
- Miglitol
- Mirabegron
- Mitomycin
- Mometasone
- Morphine
- Morphine; Naltrexone
- Nabilone
- Nadolol
- Nateglinide
- Nebivolol
- Nebivolol; Valsartan

- Nicardipine
- Nimodipine
- Nintedanib
- Nisoldipine
- Norethindrone
- Nortriptyline
- Omeprazole
- Omeprazole; Sodium Bicarbonate
- Oxybutynin
- Oxycodone
- Oxymorphone
- Paricalcitol
- Penbutolol
- Perampanel
- Perindopril; Amlodipine
- Phentermine; Topiramate
- Pindolol
- Pirfenidone
- Polatuzumab Vedotin
- Pomalidomide
- Pramlintide
- Praziquantel
- Prednisolone
- Prednisone
- Propofol
- Propoxyphene
- Propranolol
- Protriptyline
- Ramelteon
- Remifentanyl
- Repaglinide
- Retapamulin
- Rifaximin
- Riluzole
- Rocuronium
- Sacubitril; Valsartan
- Sapropterin

- Selegiline
- Selexipag
- Sibutramine
- Sitagliptin
- Sodium Bicarbonate
- Sufentanil
- Sulfonylureas
- Talazoparib
- Telotristat Ethyl
- Teniposide
- Tenofovir Alafenamide
- Tenofovir Alafenamide
- Tenofovir, PMPA
- Terbinafine
- Testosterone
- Theophylline, Aminophylline
- Thiazolidinediones
- Tiagabine
- Timolol
- Tinidazole
- Topiramate
- Trandolapril; Verapamil
- Triamcinolone
- Trimetrexate
- Trimipramine
- Ulipristal
- Upadacitinib
- Valsartan
- Verapamil
- Vinorelbine
- Yohimbine
- Zafirlukast
- Zaleplon
- Zileuton
- Zolmitriptan
- Zolpidem
- Zonisamide

Level 4 (Minor)

- Abacavir; Lamivudine, 3TC; Zidovudine, ZDV
- Atazanavir
- Atovaquone
- Atovaquone; Proguanil
- Brentuximab vedotin
- Bupivacaine
- Bupivacaine Liposomal
- Doravirine
- Fexofenadine
- Fexofenadine; Pseudoephedrine
- Indinavir
- Lamivudine, 3TC; Zidovudine, ZDV
- Levobupivacaine
- Paclitaxel
- Rabeprazole
- Somatropin, rh-GH
- Tesamorelin
- Zidovudine, ZDV

Abacavir; Lamivudine, 3TC; Zidovudine, ZDV: (Minor) Since ritonavir induces glucuronidation, there is the potential for reduction in zidovudine, ZDV plasma concentrations during concurrent therapy with ritonavir. When coadministered with ritonavir, the AUC and Cmax of zidovudine, ZDV are decreased by 12% and 27%. The clinical significance of this interaction is unknown. [28315] [47165] [58664]

Abemaciclib: (Major) If coadministration with ritonavir is necessary, reduce the dose of abemaciclib to 100 mg PO twice daily in patients on either of the recommended starting doses of either 200 mg or 150 mg twice daily. In patients who have had already had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the dose of abemaciclib to 50 mg PO twice daily. Discontinue abemaciclib for patients unable to tolerate 50 mg twice daily. If ritonavir is discontinued, increase the dose of abemaciclib to the original dose after 3 to 5 half-lives of ritonavir. Abemaciclib is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased the relative potency adjusted unbound AUC of abemaciclib plus its active metabolites (M2, M18, and M20) by 2.5-fold in cancer patients. [47165] [62393]

Acalabrutinib: (Major) Avoid the concomitant use of acalabrutinib and ritonavir; significantly increased acalabrutinib exposure may occur. Acalabrutinib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. In healthy subjects, the Cmax and AUC values of acalabrutinib were increased by 3.9-fold and 5.1-fold, respectively, when acalabrutinib was coadministered with another strong inhibitor for 5 days. [47165] [62578]

Acarbose: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. [7238] [7335]

Acebutolol: (Moderate) Cardiac and neurologic events have been reported when ritonavir was concurrently administered with beta-blockers. [5044]

Acetaminophen: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [25460] [28100] [58664]

Acetaminophen; Aspirin, ASA; Caffeine: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [25460] [28100] [58664]

Acetaminophen; Butalbital: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [28341] [46638] (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [46638] (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [25460] [28100] [58664]

Acetaminophen; Butalbital; Caffeine: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [28341] [46638] (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [46638] (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [25460] [28100] [58664]

Acetaminophen; Butalbital; Caffeine; Codeine: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [28341] [46638] (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [46638] (Moderate) Concomitant use of codeine with ritonavir may alter codeine plasma concentrations, resulting in an unpredictable effect such as reduced efficacy or symptoms of opioid withdrawal or prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage adjustment of codeine until stable drug effects are achieved. Discontinuation of ritonavir could alter codeine plasma concentrations, resulting in an unpredictable effect such as prolonged opioid adverse reactions or decreased opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to codeine. If ritonavir is discontinued, monitor the patient carefully and consider adjusting the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Ritonavir is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. CYP3A4 inhibitors may increase codeine-related adverse effects while CYP2D6 inhibitors may reduce efficacy. [33654] [34883] [47165] (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [25460] [28100] [58664]

Acetaminophen; Caffeine: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [25460] [28100] [58664]

Acetaminophen; Caffeine; Dihydrocodeine: (Moderate) Concomitant use of dihydrocodeine with ritonavir may increase dihydrocodeine plasma concentrations, resulting in greater metabolism by CYP2D6, increased dihydromorphine concentrations, and prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of dihydrocodeine until stable drug effects are achieved. Discontinuation of ritonavir could decrease dihydrocodeine plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to dihydrocodeine. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Ritonavir is a strong inhibitor of CYP3A4, an isoenzyme partially responsible for the metabolism of dihydrocodeine. [30282] [47165] (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme

CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acetaminophen; Caffeine; Magnesium Salicylate; Phenyltoloxamine: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acetaminophen; Caffeine; Phenyltoloxamine; Salicylamide: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#) (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [\[34390\]](#) [\[47165\]](#) [\[57935\]](#) [\[58664\]](#)

Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#) (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [\[34390\]](#) [\[47165\]](#) [\[57935\]](#) [\[58664\]](#)

Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#) (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [\[34390\]](#) [\[47165\]](#) [\[57935\]](#) [\[58664\]](#)

Acetaminophen; Codeine: (Moderate) Concomitant use of codeine with ritonavir may alter codeine plasma concentrations, resulting in an unpredictable effect such as reduced efficacy or symptoms of opioid withdrawal or prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage adjustment of codeine until stable drug effects are achieved. Discontinuation of ritonavir could alter codeine plasma concentrations, resulting in an unpredictable effect such as prolonged opioid adverse reactions or decreased opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to codeine. If ritonavir is discontinued, monitor the patient carefully and consider adjusting the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Ritonavir is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. CYP3A4 inhibitors may increase codeine-related adverse effects while CYP2D6 inhibitors may reduce efficacy. [\[33654\]](#) [\[34883\]](#) [\[47165\]](#) (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acetaminophen; Dextromethorphan: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acetaminophen; Dextromethorphan; Doxylamine: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acetaminophen; Dextromethorphan; Guaifenesin; Phenylephrine: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acetaminophen; Dextromethorphan; Phenylephrine: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acetaminophen; Dextromethorphan; Pseudoephedrine: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acetaminophen; Dichloralphenazone; Isometheptene: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic

isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acetaminophen; Diphenhydramine: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#) (Moderate) Concurrent administration of diphenhydramine with ritonavir may result in elevated plasma concentrations of diphenhydramine. Diphenhydramine is a CYP2D6 substrate, and ritonavir is a CYP2D6 inhibitor. Caution and close monitoring are advised if these drugs are administered together. [\[34522\]](#) [\[34523\]](#) [\[47165\]](#) [\[58664\]](#)

Acetaminophen; Guaifenesin; Phenylephrine: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acetaminophen; Hydrocodone: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [\[30379\]](#) [\[30391\]](#) [\[47165\]](#) [\[56303\]](#) [\[58531\]](#) (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acetaminophen; Oxycodone: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#) (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ritonavir is necessary. If ritonavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like ritonavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ritonavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. [\[39926\]](#) [\[47165\]](#)

Acetaminophen; Pentazocine: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acetaminophen; Propoxyphene: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#) (Moderate) Due to effects on microsomal isoenzymes responsible for hepatic metabolism, ritonavir may alter the response and/or increase the AUC of opiate analgesics. Concurrent use of ritonavir and propoxyphene is not recommended, due to the increased formation of the neurotoxic metabolites of propoxyphene. Also, propoxyphene is a substrate/inhibitor of CYP3A4. Increased serum concentrations of propoxyphene can occur from concurrent use of ritonavir, a CYP3A4 inhibitor. A reduced dosage of propoxyphene may be needed. Monitor for CNS and respiratory depression. [\[11379\]](#) [\[36008\]](#) [\[4718\]](#) [\[5044\]](#)

Acetaminophen; Pseudoephedrine: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acetaminophen; Tramadol: (Major) Tramadol is primarily metabolized by CYP2D6 and CYP3A4; drugs that inhibit these enzymes, such as ritonavir, may decrease the metabolism of tramadol. This may result in a decreased concentration of the active metabolite (O-desmethyltramadol) leading to decreased analgesic effects and possibly increased side effects (seizures and serotonin syndrome) due to higher tramadol concentrations. [\[40255\]](#) [\[5043\]](#) [\[9316\]](#) (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#)

Acidiniun; Formoterol: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [\[28318\]](#) [\[28341\]](#) [\[32901\]](#) [\[33925\]](#) [\[41231\]](#) [\[65157\]](#) [\[65170\]](#)

Adefovir: (Major) Patients who are concurrently taking adefovir with antiretrovirals like the protease inhibitors, are at risk of developing lactic acidosis and severe hepatomegaly with steatosis. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have

been reported with the use of nucleoside analogs alone or in combination with antiretrovirals. A majority of these cases have been in women; obesity and prolonged nucleoside exposure may also be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for hepatic disease; however, cases have also been reported in patients with no known risk factors. Suspend adefovir in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). [28784]

Ado-Trastuzumab emtansine: (Major) Avoid coadministration of ritonavir with ado-trastuzumab emtansine if possible due to the risk of elevated exposure to the cytotoxic component of ado-trastuzumab emtansine, DM1. Delay ado-trastuzumab emtansine treatment until ritonavir has cleared from the circulation (approximately 3 half-lives of ritonavir) when possible. If concomitant use is unavoidable, closely monitor patients for ado-trastuzumab emtansine-related adverse reactions. The cytotoxic component of ado-trastuzumab emtansine, DM1, is metabolized mainly by CYP3A4 and to a lesser extent by CYP3A5; ritonavir is a strong CYP3A4 inhibitor. Formal drug interaction studies with ado-trastuzumab emtansine have not been conducted. [28315] [53295]

Afatinib: (Moderate) If the concomitant use of ritonavir and afatinib is necessary, monitor for afatinib-related adverse reactions. If the original dose of afatinib is not tolerated, consider reducing the daily dose of afatinib by 10 mg; resume the previous dose of afatinib as tolerated after discontinuation of ritonavir. The manufacturer of afatinib recommends permanent discontinuation of therapy for severe or intolerant adverse drug reactions at a dose of 20 mg per day, but does not address a minimum dose otherwise. Afatinib is a P-glycoprotein (P-gp) substrate and ritonavir is a P-gp inhibitor; coadministration may increase plasma concentrations of afatinib. Administration with another P-gp inhibitor, given 1 hour before a single dose of afatinib, increased afatinib exposure by 48%; there was no change in afatinib exposure when the P-gp inhibitor was administered at the same time as afatinib or 6 hours later. In healthy subjects, the relative bioavailability for AUC and Cmax of afatinib was 119% and 104%, respectively, when coadministered with the same P-gp inhibitor, and 111% and 105% when the inhibitor was administered 6 hours after afatinib. [28315] [55331]

Albuterol: (Major) Avoid coadministration of lopinavir with short-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28341] [33925] [65157] [65170]

Albuterol; Ipratropium: (Major) Avoid coadministration of lopinavir with short-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28341] [33925] [65157] [65170]

Aldesleukin, IL-2: (Moderate) Concurrent administration of aldesleukin, IL-2 with ritonavir may result in increased plasma concentrations of ritonavir. Aldesleukin, IL-2 increases IL-6 concentrations, and IL-6 is an inhibitor of the hepatic isoenzyme CYP3A4; ritonavir is a substrate of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [2356] [34540] [58664]

Alfentanil: (Moderate) Alfentanil is metabolized by the hepatic isoenzyme CYP3A4. Drugs that inhibit this enzyme, such as protease inhibitors, may alter responses to alfentanil. A dose reduction of one or both drugs may be warranted. Monitor closely for oversedation and respiratory depression. [28001] [28995] [47165]

Alfuzosin: (Severe) Coadministration of alfuzosin with protease inhibitors is contraindicated due to potential hypotension. Alfuzosin is a CYP3A4 substrate and protease inhibitors are strong CYP3A4 inhibitors. [28261] [28341]

Aliskiren: (Moderate) The plasma concentrations of aliskiren may be elevated when administered concurrently with ritonavir. Clinical monitoring for adverse effects, such as decreased blood pressure, is recommended during coadministration. Ritonavir is an inhibitor of CYP3A4 and P-glycoprotein (P-gp). Aliskiren is a substrate of both CYP3A4 and P-gp. [33200] [47165] [56579]

Aliskiren; Amlodipine: (Moderate) Amlodipine is a CYP3A4 substrate. Theoretically, CYP3A4 inhibitors, such as anti-retroviral protease inhibitors, may increase the plasma concentration of amlodipine via CYP3A4 inhibition; this effect might lead to hypotension in some individuals. Caution should be used when anti-retroviral protease inhibitors are coadministered with amlodipine; therapeutic response should be monitored. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [29090] [47165] [58664]

(Moderate) The plasma concentrations of aliskiren may be elevated when administered concurrently with ritonavir. Clinical monitoring for adverse effects, such as decreased blood pressure, is recommended during coadministration. Ritonavir is an inhibitor of CYP3A4 and P-glycoprotein (P-gp). Aliskiren is a substrate of both CYP3A4 and P-gp. [33200] [47165] [56579]

Aliskiren; Amlodipine; Hydrochlorothiazide, HCTZ: (Moderate) Amlodipine is a CYP3A4 substrate. Theoretically, CYP3A4 inhibitors, such as anti-retroviral protease inhibitors, may increase the plasma concentration of amlodipine via CYP3A4 inhibition; this effect might lead to hypotension in some individuals. Caution should be used when anti-retroviral protease inhibitors are coadministered with amlodipine; therapeutic response should be monitored. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [29090] [47165] [58664]

(Moderate) The plasma concentrations of aliskiren may be elevated when administered concurrently with ritonavir. Clinical monitoring for adverse effects, such as decreased blood pressure, is recommended during coadministration. Ritonavir is an inhibitor of CYP3A4 and P-glycoprotein (P-gp). Aliskiren is a substrate of both CYP3A4 and P-gp. [33200] [47165] [56579]

Aliskiren; Hydrochlorothiazide, HCTZ: (Moderate) The plasma concentrations of aliskiren may be elevated when administered concurrently with ritonavir. Clinical monitoring for adverse effects, such as decreased blood pressure, is recommended during coadministration. Ritonavir is an inhibitor of CYP3A4 and P-glycoprotein (P-gp). Aliskiren is a substrate of both CYP3A4 and P-gp. [33200] [47165] [56579]

Aliskiren; Valsartan: (Moderate) Concurrent use of lopinavir with valsartan may result in elevated valsartan serum concentrations. Valsartan is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. Monitor for increased toxicities if these drugs are given together. [56575] [61510] [61511] [61513] (Moderate) The plasma concentrations of aliskiren may be elevated when administered concurrently with ritonavir. Clinical monitoring for adverse effects, such as decreased blood pressure, is recommended during coadministration. Ritonavir is an inhibitor of CYP3A4 and P-glycoprotein (P-gp). Aliskiren is a substrate of both CYP3A4 and P-gp. [33200] [47165] [56579] (Minor) Valsartan is a substrate of the hepatic efflux transporter MRP2 and ritonavir is an inhibitor of MRP2. Coadministration may increase systemic exposure to valsartan. Patients should be monitored for adverse effects of valsartan during coadministration. [28315] [29130] [36646] [39870] [60860]

Almotriptan: (Major) Ritonavir may increase the systemic exposure of almotriptan. If coadministered, the recommended starting dose of almotriptan is 6.25 mg; do not exceed 12.5 mg within a 24-hour period. Avoid coadministration in patients with renal or hepatic impairment. Almotriptan is a CYP3A4 substrate and ritonavir is a potent CYP3A4 inhibitor. In a drug interaction study, coadministration of almotriptan and ketoconazole, another potent CYP3A4 inhibitor, resulted in an approximately 60% increase in almotriptan exposure. [28001] [31869]

Alogliptin: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [7238] [7335]

Alogliptin; Metformin: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [7238] [7335] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Alogliptin; Pioglitazone: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [7238] [7335]

Alosetron: (Major) Concurrent administration of alosetron with ritonavir may alter alosetron plasma concentrations; however, the precise effect is undefined. Alosetron is metabolized by the hepatic isoenzymes CYP3A4, CYP2C9, and CYP1A2; ritonavir is an inhibitor of CYP3A4 and an inducer of CYP1A2 and possibly CYP2C9. Caution and close monitoring are advised if these drugs are administered together. [28382] [5044]

Alpha-glucosidase Inhibitors: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. [7238] [7335]

Alprazolam: (Major) Coadministration of alprazolam and ritonavir or lopinavir; ritonavir is not recommended. If coadministration cannot be avoided, a dosage reduction of alprazolam should be considered. Lopinavir and ritonavir are potent CYP3A4 inhibitors. The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome CYP3A. Drugs that inhibit this metabolic pathway may profoundly decrease alprazolam clearance, resulting in increased potential for serious alprazolam-related adverse events, such as respiratory depression and prolonged sedation. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A isoenzymes. [28040] [28341] [47165]

Amiodarone: (Major) Avoid coadministration of lopinavir with amiodarone due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Amiodarone, a Class III antiarrhythmic agent, is associated with a well-established risk of QT prolongation and torsade de pointes (TdP). Although the frequency of TdP is less with amiodarone than with other Class III agents, amiodarone is still associated with a risk of TdP. Due to the extremely long half-life of amiodarone, a drug interaction is possible for days to weeks after discontinuation of amiodarone. [28224] [28341] [28432] [28457] [65157] [65170] (Major) Coadministration of HIV treatment doses of ritonavir and amiodarone is contraindicated due to the potential for serious or life-threatening reactions, such as cardiac arrhythmias. Cautious consideration may be given to administering amiodarone with boosting doses of ritonavir. Ritonavir is an inhibitor of CYP3A4 and increased plasma concentrations of drugs extensively metabolized by this enzyme, such as amiodarone, should be expected with concurrent use. [47165]

Amitriptyline: (Moderate) A dose reduction of the tricyclic antidepressant (TCA) may be necessary when coadministered with ritonavir. Concurrent use may result in elevated TCA plasma concentrations. [47165]

Amitriptyline; Chlordiazepoxide: (Major) CYP3A4 inhibitors, such as protease inhibitors, may reduce the metabolism of chlordiazepoxide and increase the potential for benzodiazepine toxicity. A decrease in the chlordiazepoxide dose may be needed. [32432] [5286] (Moderate) A dose reduction of the tricyclic antidepressant (TCA) may be necessary when coadministered with ritonavir. Concurrent use may result in elevated TCA plasma concentrations. [47165]

Amlodipine: (Moderate) Amlodipine is a CYP3A4 substrate. Theoretically, CYP3A4 inhibitors, such as anti-retroviral protease inhibitors, may increase the plasma concentration of amlodipine via CYP3A4 inhibition; this effect might lead to hypotension in some individuals. Caution should be used when anti-retroviral protease inhibitors are coadministered with amlodipine; therapeutic response should be monitored. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [29090] [47165] [58664]

Amlodipine; Atorvastatin: (Major) Use caution and the lowest atorvastatin dose necessary if atorvastatin must be coadministered with ritonavir. The risk of developing myopathy/rhabdomyolysis increases when atorvastatin is used concomitantly with ritonavir. Monitor patients for any signs or symptoms of muscle pain, weakness, or tenderness especially in the initial months of therapy and any time the dosage of either drug is titrated upward. Protease inhibitors inhibit the CYP3A4 metabolism of atorvastatin. The serious risk of myopathy or rhabdomyolysis should be weighed carefully against the benefits of combined 'statin' and lopinavir; ritonavir therapy; there is no assurance that periodic monitoring of CK will prevent the occurrence of severe myopathy and renal damage. [43900] (Major) Use caution and the lowest atorvastatin dose necessary if coadministration with lopinavir; ritonavir is necessary due to an increased risk of myopathy and rhabdomyolysis. Carefully weigh the potential benefits and risk of combined therapy. Use the lowest possible atorvastatin dose. Closely monitor patients for signs and symptoms of muscle pain, tenderness, or weakness especially during the initial months of therapy and during upward titration of either drug. There is no assurance that period monitoring of creatinine phosphokinase (CPK) will prevent the occurrence of myopathy. Protease inhibitors inhibit the CYP3A4 metabolism of atorvastatin. In addition, atorvastatin is a substrate of the drug transporter organic anion transporting polypeptide (OATP1B1); lopinavir is an OATP1B1 inhibitor. [28341] [28729] [34503] [41275] [61510] [61511] [61513] (Moderate) Amlodipine is a CYP3A4 substrate. Theoretically, CYP3A4 inhibitors, such as anti-retroviral protease inhibitors, may increase the plasma concentration of amlodipine via CYP3A4 inhibition; this effect might lead to hypotension in some individuals. Caution should be used when anti-retroviral protease inhibitors are coadministered with amlodipine; therapeutic response should be monitored. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [29090] [47165] [58664]

Amlodipine; Benazepril: (Moderate) Amlodipine is a CYP3A4 substrate. Theoretically, CYP3A4 inhibitors, such as anti-retroviral protease inhibitors, may increase the plasma concentration of amlodipine via CYP3A4 inhibition; this effect might lead to hypotension in some individuals. Caution should be used when anti-retroviral protease inhibitors are coadministered with amlodipine; therapeutic response should be monitored. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [29090] [47165] [58664]

Amlodipine; Celecoxib: (Moderate) Amlodipine is a CYP3A4 substrate. Theoretically, CYP3A4 inhibitors, such as anti-retroviral protease inhibitors, may increase the plasma concentration of amlodipine via CYP3A4 inhibition; this effect might lead to hypotension in some individuals. Caution should be used when anti-retroviral protease inhibitors are coadministered with amlodipine; therapeutic response should be monitored. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [29090] [47165] [58664]

Amlodipine; Hydrochlorothiazide, HCTZ; Olmesartan: (Moderate) Amlodipine is a CYP3A4 substrate. Theoretically, CYP3A4 inhibitors, such as anti-retroviral protease inhibitors, may increase the plasma concentration of amlodipine via CYP3A4 inhibition; this effect might lead to hypotension in some individuals. Caution should be used when anti-retroviral protease inhibitors are coadministered with amlodipine; therapeutic response should be monitored. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [29090] [47165] [58664]

Amlodipine; Hydrochlorothiazide, HCTZ; Valsartan: (Moderate) Amlodipine is a CYP3A4 substrate. Theoretically, CYP3A4 inhibitors, such as anti-retroviral protease inhibitors, may increase the plasma concentration of amlodipine via CYP3A4 inhibition; this effect might lead to hypotension in some individuals. Caution should be used when anti-retroviral protease inhibitors are coadministered with amlodipine; therapeutic response should be monitored. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [29090] [47165] [58664] (Moderate) Concurrent use of lopinavir with valsartan may result in elevated valsartan serum concentrations. Valsartan is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. Monitor for increased toxicities if these drugs are given together. [56575] [61510] [61511] [61513] (Minor) Valsartan is a substrate of the hepatic efflux transporter MRP2 and ritonavir is an inhibitor of MRP2. Coadministration may increase systemic exposure to valsartan. Patients should be monitored for adverse effects of valsartan during coadministration. [28315] [29130] [36646] [39870] [60860]

Amlodipine; Olmesartan: (Moderate) Amlodipine is a CYP3A4 substrate. Theoretically, CYP3A4 inhibitors, such as anti-retroviral protease inhibitors, may increase the plasma concentration of amlodipine via CYP3A4 inhibition; this effect might lead to hypotension in some individuals. Caution should be used when anti-retroviral protease inhibitors are coadministered with amlodipine; therapeutic response should be monitored. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of

coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [29090] [47165] [58664]

Amlodipine; Telmisartan: (Moderate) Amlodipine is a CYP3A4 substrate. Theoretically, CYP3A4 inhibitors, such as anti-retroviral protease inhibitors, may increase the plasma concentration of amlodipine via CYP3A4 inhibition; this effect might lead to hypotension in some individuals. Caution should be used when anti-retroviral protease inhibitors are coadministered with amlodipine; therapeutic response should be monitored. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [29090] [47165] [58664]

Amlodipine; Valsartan: (Moderate) Amlodipine is a CYP3A4 substrate. Theoretically, CYP3A4 inhibitors, such as anti-retroviral protease inhibitors, may increase the plasma concentration of amlodipine via CYP3A4 inhibition; this effect might lead to hypotension in some individuals. Caution should be used when anti-retroviral protease inhibitors are coadministered with amlodipine; therapeutic response should be monitored. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [29090] [47165] [58664] (Moderate) Concurrent use of lopinavir with valsartan may result in elevated valsartan serum concentrations. Valsartan is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. Monitor for increased toxicities if these drugs are given together. [56575] [61510] [61511] [61513] (Minor) Valsartan is a substrate of the hepatic efflux transporter MRP2 and ritonavir is an inhibitor of MRP2. Coadministration may increase systemic exposure to valsartan. Patients should be monitored for adverse effects of valsartan during coadministration. [28315] [29130] [36646] [39870] [60860]

Amobarbital: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [28341] [46638] (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [46638]

Amoxapine: (Major) Ritonavir potentially inhibits CYP2D6, and may inhibit the metabolism of amoxapine. Since the magnitude of the interaction with the amoxapine is difficult to predict but may be significant, monitor patients receiving ritonavir and amoxapine concurrently closely. Adjust the dosage of the coadministered drug based on therapeutic response. Amoxapine serum concentration monitoring may be useful to guide adjustments and prevent toxicity. [28558] [46638] [47165]

Amoxicillin; Clarithromycin; Lansoprazole: (Major) Avoid coadministration of lopinavir with clarithromycin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Clarithromycin is associated with an established risk for QT prolongation and torsade de pointes (TdP). [28225] [28238] [28341] [28413] [28419] [65157] [65170] (Major) Because the exposure to 14-OH clarithromycin is significantly decreased by ritonavir, consider alternative antibiotic therapy for indications other than *Mycobacterium avium*. Clarithromycin doses above 1000 mg should not be administered with ritonavir. If coadministration cannot be avoided, clarithromycin dosage reductions are recommended in patients with renal impairment (CrCl 30 to 60 mL/minute, decrease clarithromycin by 50%; CrCl less than 30 mL/minute, decrease clarithromycin by 75%). Concomitant administration of ritonavir and clarithromycin resulted in a 77% increase in clarithromycin exposure and a 100% decrease in 14-OH clarithromycin exposure. The microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria. [28238] [46638] [47165] (Moderate) Increased exposure to lansoprazole may occur during concurrent administration of ritonavir. Although dosage adjustment of lansoprazole is not normally required, dosage reduction may be considered in patients receiving higher lansoprazole doses (e.g., those with Zollinger-Ellison syndrome). Ritonavir is a strong CYP3A4 inhibitor. Lansoprazole is a CYP2C19 and CYP3A4 substrate. Coadministration of a dual CYP2C19/strong CYP3A4 inhibitor increased the lansoprazole AUC by an average of 4-times. [40596] [47165]

Amoxicillin; Clarithromycin; Omeprazole: (Major) Avoid coadministration of lopinavir with clarithromycin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Clarithromycin is associated with an established risk for QT prolongation and torsade de pointes (TdP). [28225] [28238] [28341] [28413] [28419] [65157] [65170] (Major) Because the exposure to 14-OH clarithromycin is significantly decreased by ritonavir, consider alternative antibiotic therapy for indications other than *Mycobacterium avium*. Clarithromycin doses above 1000 mg should not be administered with ritonavir. If coadministration cannot be avoided, clarithromycin dosage reductions are recommended in patients with renal impairment (CrCl 30 to 60 mL/minute, decrease clarithromycin by 50%; CrCl less than 30 mL/minute, decrease clarithromycin by 75%). Concomitant administration of ritonavir and clarithromycin resulted in a 77% increase in clarithromycin exposure and a 100% decrease in 14-OH clarithromycin exposure. The microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria. [28238] [46638] [47165] (Moderate) Increased exposure to omeprazole may occur during concurrent administration of ritonavir. Although dosage adjustment of omeprazole is not normally required, dosage reduction may be considered in patients receiving higher omeprazole doses (e.g., those with Zollinger-Ellison syndrome). Ritonavir is a strong CYP3A4 inhibitor. Omeprazole is a CYP2C19 and CYP3A4 substrate. Coadministration of a dual CYP2C19/strong CYP3A4 inhibitor increased the omeprazole AUC by an average of 4-times. [29564] [47165]

Amphetamine: (Moderate) Warn patients that the risk of amphetamine toxicity may be increased during concurrent use of ritonavir, a strong CYP2D6 inhibitor. Amphetamines are partially metabolized by CYP2D6 and have serotonergic properties; inhibition of amphetamine metabolism may increase the risk of serotonin syndrome or other toxicity. If serotonin syndrome occurs, both the

amphetamine and CYP2D6 inhibitor should be discontinued and appropriate medical treatment should be implemented. [25887] [29219] [33263] [47165] [57067]

Amphetamine; Dextroamphetamine: (Moderate) Warn patients that the risk of amphetamine toxicity may be increased during concurrent use of ritonavir, a strong CYP2D6 inhibitor. Amphetamines are partially metabolized by CYP2D6 and have serotonergic properties; inhibition of amphetamine metabolism may increase the risk of serotonin syndrome or other toxicity. If serotonin syndrome occurs, both the amphetamine and CYP2D6 inhibitor should be discontinued and appropriate medical treatment should be implemented. [25887] [29219] [33263] [47165] [57067]

Amphetamines: (Moderate) Warn patients that the risk of amphetamine toxicity may be increased during concurrent use of ritonavir, a strong CYP2D6 inhibitor. Amphetamines are partially metabolized by CYP2D6 and have serotonergic properties; inhibition of amphetamine metabolism may increase the risk of serotonin syndrome or other toxicity. If serotonin syndrome occurs, both the amphetamine and CYP2D6 inhibitor should be discontinued and appropriate medical treatment should be implemented. [25887] [29219] [33263] [47165] [57067]

Anagrelide: (Major) Avoid coadministration of lopinavir with anagrelide due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Torsade de pointes (TdP) and ventricular tachycardia have been reported with anagrelide. In addition, dose-related increases in mean QTc and heart rate were observed in healthy subjects. [28341] [30163] [65157] [65170]

Apalutamide: (Severe) Coadministration of lopinavir; ritonavir with apalutamide is contraindicated. Taking these drugs together could decrease lopinavir concentrations, and may lead to a reduction in antiretroviral activity; apalutamide exposure may also increase. Lopinavir; ritonavir is a CYP3A4 substrate and strong inhibitor. Apalutamide is a CYP3A4 substrate and strong inducer. [28341] [56579] [62874] (Severe) Coadministration of ritonavir with apalutamide is contraindicated as there is a potential for decreased ritonavir concentrations which may lead to a reduction of antiretroviral efficacy and the potential development of viral resistance; exposure to apalutamide may also increase. Ritonavir is a CYP3A4 substrate and strong inhibitor. Apalutamide is a CYP3A4 substrate and strong inducer. [47165] [62874]

Apixaban: (Major) Reduce the apixaban dose by 50% when coadministered with drugs that are both strong inhibitors of CYP3A4 and P-gp, such as ritonavir. If patients are already receiving the reduced dose of 2.5 mg twice daily, avoid concomitant administration of apixaban and ritonavir. Concomitant administration of ritonavir and apixaban results in increased exposure to apixaban and an increase in the risk of bleeding. [52739]

Apomorphine: (Major) Avoid coadministration of lopinavir; ritonavir with apomorphine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Limited data indicate that QT prolongation is possible with apomorphine administration; the change in QTc interval is not significant in most patients receiving dosages within the manufacturer's guidelines. [28341] [28661] [65157] [65170]

Aprepitant, Fosaprepitant: (Major) Avoid the concomitant use of lopinavir with aprepitant, fosaprepitant due to substantially increased exposure of aprepitant; increased lopinavir exposure may also occur for several days after administration of a multi-day regimen of oral aprepitant. Lopinavir is a strong CYP3A4 inhibitor and aprepitant is a CYP3A4 substrate. Coadministration of a single oral dose of aprepitant (125 mg) on day 5 of a 10-day ketoconazole regimen (strong CYP3A4 inhibitor) increased the aprepitant AUC approximately 5-fold, and increased the mean terminal half-life by approximately 3-fold. Lopinavir is also a CYP3A4 substrate. Aprepitant, when administered as a 3-day oral regimen (125 mg/80 mg/80 mg), is a moderate CYP3A4 inhibitor and inducer and may additionally increase plasma concentrations of lopinavir. For example, a 5-day oral aprepitant regimen increased the AUC of another CYP3A4 substrate, midazolam (single dose), by 2.3-fold on day 1 and by 3.3-fold on day 5. After a 3-day oral aprepitant regimen, the AUC of midazolam (given on days 1, 4, 8, and 15) increased by 25% on day 4, and then decreased by 19% and 4% on days 8 and 15, respectively. As a single 125 mg or 40 mg oral dose, the inhibitory effect of aprepitant on CYP3A4 is weak, with the AUC of midazolam increased by 1.5-fold and 1.2-fold, respectively. After administration, fosaprepitant is rapidly converted to aprepitant and shares many of the same drug interactions. However, as a single 150 mg intravenous dose, fosaprepitant only weakly inhibits CYP3A4 for a duration of 2 days; there is no evidence of CYP3A4 induction. Fosaprepitant 150 mg IV as a single dose increased the AUC of midazolam (given on days 1 and 4) by approximately 1.8-fold on day 1; there was no effect on day 4. Less than a 2-fold increase in the midazolam AUC is not considered clinically important. [28341] [30676] [40027] [47165] [56579] (Major) Avoid the concomitant use of ritonavir with aprepitant, fosaprepitant due to substantially increased exposure of aprepitant; after administration, fosaprepitant is rapidly converted to aprepitant and shares many of the same drug interactions. Increased ritonavir exposure may also occur. If coadministration cannot be avoided, use caution and monitor for an increase in ritonavir- and aprepitant-related adverse effects for several days after administration of a multi-day aprepitant regimen. Ritonavir is a strong CYP3A4 inhibitor and aprepitant is a CYP3A4 substrate. Coadministration with another strong CYP3A4 inhibitor increased the AUC of aprepitant by approximately 5-fold, and the mean terminal half-life by approximately 3-fold. Ritonavir is also a CYP3A4 substrate. Aprepitant, when administered as a 3-day oral regimen (125 mg/80 mg/80 mg), is a moderate CYP3A4 inhibitor. When administered as a single oral or single intravenous dose, the inhibitory effect of aprepitant on CYP3A4 is weak and does not result in a clinically significant increase in the AUC of a sensitive substrate. [30676] [40027] [47165]

Arformoterol: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28318] [28341] [32901] [33925] [41231] [65157] [65170] (Moderate) The use of ritonavir could result in QT prolongation. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with ritonavir, include beta-agonists. [28318] [33925] [41231] [47165]

Aripiprazole: (Major) Avoid coadministration of lopinavir with aripiprazole due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid

any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. QT prolongation has occurred during therapeutic use of aripiprazole and following overdose. [28341] [42845] [65157] [65170] (Major) Because aripiprazole is metabolized by CYP3A4 and CYP2D6, the manufacturer recommends that the oral aripiprazole dose be reduced to one-quarter (25%) of the usual dose in patients receiving inhibitors of both CYP3A4 and CYP2D6 such as ritonavir. Patients classified as CYP2D6 poor metabolizers (PMs) who are receiving a strong CYP3A4 inhibitor should have their oral aripiprazole dose reduced to one-quarter (25%) of the usual dose with subsequent adjustments based upon clinical response. Adults receiving a combination of a CYP3A4 and CYP2D6 inhibitor for more than 14 days should have their Abilify Maintena dose reduced from 400 mg/month to 200 mg/month or from 300 mg/month to 160 mg/month, respectively. Adults receiving Abilify Maintena who are PMs and receiving a strong CYP3A4 inhibitor, such as ritonavir, should have a dose reduction to 200 mg/month IM. In adults receiving Aristada, the Aristada dose should be reduced to the next lower strength during use of a strong CYP3A4 inhibitor for more than 14 days. For patients receiving 882 mg of Aristada every 6 weeks or 1064 mg every 2 months, the next lower strength should be 441 mg administered every 4 weeks. No dosage adjustment is necessary in patients taking 441 mg IM of Aristada, if tolerated. Adults receiving Aristada who are PMs of CYP2D6 and receiving a strong CYP3A4 inhibitor for more than 14 days should have their dose reduced from 662 mg, 882 mg, or 1064 mg to 441 mg IM; no dose adjustment is needed in patients receiving 441 mg of Aristada, if tolerated. In adults receiving Aristada 662 mg, 882 mg, or 1064 mg, combined use of a strong CYP2D6 inhibitor and a strong CYP3A4 inhibitor for more than 14 days should be avoided; no dose adjustment is needed in patients taking 441 mg, if tolerated. Avoid concurrent use of Aristada Initio and strong CYP3A4 inhibitors because the dose of Aristada Initio cannot be modified. [28341] [42845] [47165] [53394] [60196] [63328]

Armodafinil: (Major) Coadministration of ritonavir with armodafinil may result in elevated armodafinil concentrations and decreased ritonavir concentrations. Decreased antiretroviral concentrations may lead to a reduction of antiretroviral efficacy and the potential development of viral resistance. Armodafinil is a substrate and inducer of CYP3A4, and a P-glycoprotein (P-gp) substrate. Ritonavir is a substrate of CYP3A4 and an inhibitor of P-gp. Ritonavir is also a potent inhibitor of CYP3A4. [33467] [47165]

Arsenic Trioxide: (Major) Avoid coadministration of lopinavir with arsenic trioxide due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Torsade de pointes (TdP), QT interval prolongation, and complete atrioventricular block have been reported with arsenic trioxide use. [28226] [28341] [28432] [28457] [65157] [65170]

Artemether; Lumefantrine: (Major) Avoid coadministration of lopinavir with artemether; lumefantrine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs are associated with QT prolongation. [28341] [35401] [5162] [65157] [65170] (Major) Avoid coadministration of lopinavir with artemether; lumefantrine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs are associated with QT prolongation. [28341] [35401] [65157] [65170] (Major) Ritonavir is a substrate, potent inhibitor, and inducer of the CYP3A4 isoenzyme, depending on the activity of the coadministered drug. Both components of artemether; lumefantrine are substrates of the CYP3A4 isoenzyme; therefore, coadministration may lead to increased or decreased artemether; lumefantrine concentrations. Concomitant use warrants caution due to the potential for increased side effects, including increased potentiation of QT prolongation due to increased drug concentrations, or loss of antimalarial activity depending on the artemether; lumefantrine concentrations. Consider ECG monitoring if ritonavir must be used with or after artemether; lumefantrine treatment. [11416] [35401] [4194] [47165] [5044] [5110] (Major) Ritonavir is a substrate, potent inhibitor, and inducer of the CYP3A4 isoenzyme, depending on the activity of the coadministered drug. Both components of artemether; lumefantrine are substrates of the CYP3A4 isoenzyme; therefore, coadministration may lead to increased or decreased artemether; lumefantrine concentrations. Concomitant use warrants caution due to the potential for increased side effects, including increased potentiation of QT prolongation due to increased drug concentrations, or loss of antimalarial activity depending on the artemether; lumefantrine concentrations. Consider ECG monitoring if ritonavir must be used with or after artemether; lumefantrine treatment. [11416] [35401] [4194] [5044] [5110] [60002]

Asenapine: (Major) Avoid coadministration of lopinavir with asenapine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [28341] [36343] [65157] [65170]

Aspirin, ASA; Butalbital; Caffeine: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [28341] [46638] (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [46638]

Aspirin, ASA; Butalbital; Caffeine; Codeine: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [28341] [46638] (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [46638] (Moderate) Concomitant use of codeine with ritonavir may alter codeine plasma concentrations, resulting in an unpredictable effect such as reduced efficacy or symptoms of opioid withdrawal or prolonged opioid adverse reactions, including hypotension, respiratory depression,

profound sedation, coma, and death. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage adjustment of codeine until stable drug effects are achieved. Discontinuation of ritonavir could alter codeine plasma concentrations, resulting in an unpredictable effect such as prolonged opioid adverse reactions or decreased opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to codeine. If ritonavir is discontinued, monitor the patient carefully and consider adjusting the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Ritonavir is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. CYP3A4 inhibitors may increase codeine-related adverse effects while CYP2D6 inhibitors may reduce efficacy. [33654] [34883] [47165]

Aspirin, ASA; Caffeine; Dihydrocodeine: (Moderate) Concomitant use of dihydrocodeine with ritonavir may increase dihydrocodeine plasma concentrations, resulting in greater metabolism by CYP2D6, increased dihydromorphine concentrations, and prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of dihydrocodeine until stable drug effects are achieved. Discontinuation of ritonavir could decrease dihydrocodeine plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to dihydrocodeine. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Ritonavir is a strong inhibitor of CYP3A4, an isoenzyme partially responsible for the metabolism of dihydrocodeine. [30282] [47165]

Aspirin, ASA; Carisoprodol; Codeine: (Moderate) Concomitant use of codeine with ritonavir may alter codeine plasma concentrations, resulting in an unpredictable effect such as reduced efficacy or symptoms of opioid withdrawal or prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage adjustment of codeine until stable drug effects are achieved. Discontinuation of ritonavir could alter codeine plasma concentrations, resulting in an unpredictable effect such as prolonged opioid adverse reactions or decreased opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to codeine. If ritonavir is discontinued, monitor the patient carefully and consider adjusting the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Ritonavir is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. CYP3A4 inhibitors may increase codeine-related adverse effects while CYP2D6 inhibitors may reduce efficacy. [33654] [34883] [47165]

Aspirin, ASA; Citric Acid; Sodium Bicarbonate: (Moderate) Concurrent administration of tipranavir and ritonavir with antacids results in decreased tipranavir concentrations. Administer tipranavir and ritonavir 2 hours before or 1 hour after antacids. [1800] [1802]

Aspirin, ASA; Omeprazole: (Moderate) Increased exposure to omeprazole may occur during concurrent administration of ritonavir. Although dosage adjustment of omeprazole is not normally required, dosage reduction may be considered in patients receiving higher omeprazole doses (e.g., those with Zollinger-Ellison syndrome). Ritonavir is a strong CYP3A4 inhibitor. Omeprazole is a CYP2C19 and CYP3A4 substrate. Coadministration of a dual CYP2C19/strong CYP3A4 inhibitor increased the omeprazole AUC by an average of 4-times. [29564] [47165]

Aspirin, ASA; Oxycodone: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ritonavir is necessary. If ritonavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like ritonavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ritonavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. [39926] [47165]

Atazanavir: (Minor) Coadministration of atazanavir with ritonavir results in higher atazanavir concentrations; reduced adult doses of atazanavir 300 mg once daily are recommended when ritonavir (100 mg once daily) is given concomitantly. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including atazanavir) has not been evaluated. Atazanavir is a CYP3A4 substrate; ritonavir is a strong inhibitor of CYP3A4. [28142] [28315]

Atazanavir; Cobicistat: (Severe) Use of ritonavir with cobicistat is not recommended, because of similar effects on CYP3A. Both ritonavir and cobicistat are potent inhibitors of CYP3A4. [51664] [58000] [58761] [58763] (Minor) Coadministration of atazanavir with ritonavir results in higher atazanavir concentrations; reduced adult doses of atazanavir 300 mg once daily are recommended when ritonavir (100 mg once daily) is given concomitantly. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including atazanavir) has not been evaluated. Atazanavir is a CYP3A4 substrate; ritonavir is a strong inhibitor of CYP3A4. [28142] [28315]

Atenolol: (Moderate) Cardiac and neurologic events have been reported when ritonavir was concurrently administered with beta-blockers. [5044]

Atenolol; Chlorthalidone: (Moderate) Cardiac and neurologic events have been reported when ritonavir was concurrently administered with beta-blockers. [5044]

Atomoxetine: (Major) Avoid coadministration of lopinavir with atomoxetine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. QT prolongation has occurred during therapeutic use of atomoxetine and following overdose. [28341] [28405] [65157] [65170]

Atorvastatin: (Major) Use caution and the lowest atorvastatin dose necessary if atorvastatin must be coadministered with ritonavir. The risk of developing myopathy/rhabdomyolysis increases when atorvastatin is used concomitantly with ritonavir. Monitor patients for any signs or symptoms of muscle pain, weakness, or tenderness especially in the initial months of therapy and any time the dosage of either drug is titrated upward. Protease inhibitors inhibit the CYP3A4 metabolism of atorvastatin. The serious risk of myopathy or rhabdomyolysis should be weighed carefully against the benefits of combined 'statin' and lopinavir; ritonavir therapy; there is no

assurance that periodic monitoring of CK will prevent the occurrence of severe myopathy and renal damage. [43900] (Major) Use caution and the lowest atorvastatin dose necessary if coadministration with lopinavir; ritonavir is necessary due to an increased risk of myopathy and rhabdomyolysis. Carefully weigh the potential benefits and risk of combined therapy. Use the lowest possible atorvastatin dose. Closely monitor patients for signs and symptoms of muscle pain, tenderness, or weakness especially during the initial months of therapy and during upward titration of either drug. There is no assurance that period monitoring of creatinine phosphokinase (CPK) will prevent the occurrence of myopathy. Protease inhibitors inhibit the CYP3A4 metabolism of atorvastatin. In addition, atorvastatin is a substrate of the drug transporter organic anion transporting polypeptide (OATP1B1); lopinavir is an OATP1B1 inhibitor. [28341] [28729] [34503] [41275] [61510] [61511] [61513]

Atorvastatin; Ezetimibe: (Major) Use caution and the lowest atorvastatin dose necessary if atorvastatin must be coadministered with ritonavir. The risk of developing myopathy/rhabdomyolysis increases when atorvastatin is used concomitantly with ritonavir. Monitor patients for any signs or symptoms of muscle pain, weakness, or tenderness especially in the initial months of therapy and any time the dosage of either drug is titrated upward. Protease inhibitors inhibit the CYP3A4 metabolism of atorvastatin. The serious risk of myopathy or rhabdomyolysis should be weighed carefully against the benefits of combined 'statin' and lopinavir; ritonavir therapy; there is no assurance that periodic monitoring of CK will prevent the occurrence of severe myopathy and renal damage. [43900] (Major) Use caution and the lowest atorvastatin dose necessary if coadministration with lopinavir; ritonavir is necessary due to an increased risk of myopathy and rhabdomyolysis. Carefully weigh the potential benefits and risk of combined therapy. Use the lowest possible atorvastatin dose. Closely monitor patients for signs and symptoms of muscle pain, tenderness, or weakness especially during the initial months of therapy and during upward titration of either drug. There is no assurance that period monitoring of creatinine phosphokinase (CPK) will prevent the occurrence of myopathy. Protease inhibitors inhibit the CYP3A4 metabolism of atorvastatin. In addition, atorvastatin is a substrate of the drug transporter organic anion transporting polypeptide (OATP1B1); lopinavir is an OATP1B1 inhibitor. [28341] [28729] [34503] [41275] [61510] [61511] [61513]

Atovaquone: (Minor) Concurrent administration of lopinavir; ritonavir with atovaquone; proguanil has shown to decrease the atovaquone AUC by 74% and the proguanil AUC by 38%. Consider alternative malaria prophylaxis. [28341] [46638] (Minor) The concurrent administration of ritonavir with atovaquone may result in decreased plasma levels of atovaquone. The clinical significance and mechanism of this potential interaction are unknown; the manufacturer states that an increase in atovaquone doses may be needed. [28315] [28341] [46638] [58664]

Atovaquone; Proguanil: (Minor) Concurrent administration of lopinavir; ritonavir with atovaquone; proguanil has shown to decrease the atovaquone AUC by 74% and the proguanil AUC by 38%. Consider alternative malaria prophylaxis. [28341] [46638] (Minor) The concurrent administration of ritonavir with atovaquone may result in decreased plasma levels of atovaquone. The clinical significance and mechanism of this potential interaction are unknown; the manufacturer states that an increase in atovaquone doses may be needed. [28315] [28341] [46638] [58664]

Atropine; Hyoscyamine; Phenobarbital; Scopolamine: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [28341] [46638] (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [46638]

Avanafil: (Major) Avanafil is a substrate of and primarily metabolized by CYP3A4. Studies have shown that drugs that inhibit CYP3A4 can increase avanafil exposure. Patients taking strong CYP3A4 inhibitors such as ritonavir, should not take avanafil. For example, ketoconazole increased avanafil AUC and C_{max} equal to 13-fold and 3-fold, respectively and prolonged the half-life of avanafil to approximately 9 hours. Likewise, coadministration of ritonavir with avanafil resulted in an approximate 13-fold increase in AUC and 2.4-fold increase in C_{max} of avanafil. Therefore, concomitant use with strong CYP3A4 inhibitors is not recommended. [28315] [47165] [49866]

Avapritinib: (Major) Avoid coadministration of avapritinib with ritonavir due to the risk of increased avapritinib-related adverse reactions. Avapritinib is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor is predicted to increase the AUC of avapritinib by 600% at steady-state. [47165] [64922]

Avatrombopag: (Major) In patients with chronic immune thrombocytopenia (ITP), increase the starting dose of avatrombopag to 40 mg PO once daily when used concomitantly with ritonavir. In patients starting ritonavir while receiving avatrombopag, monitor platelet counts and adjust the avatrombopag dose as necessary. Dosage adjustments are not required for patients with chronic liver disease. Avatrombopag is a CYP2C9 and CYP3A4 substrate, and dual moderate or strong inducers such as ritonavir decrease avatrombopag exposure, which may reduce efficacy. [47165] [63175]

Axitinib: (Major) Avoid coadministration of axitinib with ritonavir due to the risk of increased axitinib-related adverse reactions. If coadministration is unavoidable, decrease the dose of axitinib by approximately half; subsequent doses can be increased or decreased based on individual safety and tolerability. Resume the original dose of axitinib approximately 3 to 5 half-lives after ritonavir is discontinued. Axitinib is a CYP3A4/5 substrate and ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4/5 inhibitor significantly increased the plasma exposure of axitinib in healthy volunteers. [47165] [48494]

Azelastine; Fluticasone: (Major) Coadministration of inhaled fluticasone propionate and ritonavir is not recommended; use caution with inhaled fluticasone furoate. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving inhaled fluticasone propionate with ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Fluticasone is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. In a drug interaction study, coadministration with ritonavir increased plasma fluticasone propionate exposure resulting in an 86% decrease in serum cortisol AUC. Another strong inhibitor increased fluticasone furoate exposure by 1.33-fold with a 27% reduction in weighted mean serum cortisol; this change does not necessitate dose adjustment of fluticasone furoate. [40360] [40475] [43972] [57805]

Azithromycin: (Major) Avoid coadministration of azithromycin with lopinavir; ritonavir due to the increased risk of QT prolongation. If use together is necessary, obtain an ECG at baseline to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. QT prolongation and torsade de pointes (TdP) have been spontaneously reported during azithromycin postmarketing surveillance. Lopinavir; ritonavir is associated with QT prolongation. [\[28341\]](#) [\[28855\]](#) [\[43974\]](#) [\[65157\]](#) [\[65170\]](#)

Barbiturates: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [\[28341\]](#) [\[46638\]](#) (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [\[46638\]](#)

Bedaquiline: (Major) Avoid coadministration of lopinavir with bedaquiline due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Discontinue bedaquiline if evidence of serious ventricular arrhythmia or QTcF interval more than 500 msec. Both drugs are associated with QT prolongation. [\[28341\]](#) [\[52746\]](#) [\[65157\]](#) [\[65170\]](#) (Major) Concurrent use of bedaquiline and ritonavir should be avoided due to the potential risk of adverse reactions to bedaquiline because of increased systemic exposure. Bedaquiline is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Concurrent use of another strong CYP3A4 inhibitor increased bedaquiline exposure by 22%. [\[47165\]](#) [\[52746\]](#)

Belladonna Alkaloids; Ergotamine; Phenobarbital: (Severe) Coadministration of ergot alkaloids with potent inhibitors of CYP3A4, like anti-retroviral protease inhibitors is considered contraindicated due to the risk of acute ergot toxicity (e.g., vasospasm leading to cerebral ischemia, peripheral ischemia and/or other serious effects). Several case reports have established the clinical significance of this interaction in the medical literature. In some cases, fatal interactions have occurred. [\[28142\]](#) [\[28341\]](#) [\[28731\]](#) [\[28839\]](#) [\[28995\]](#) [\[32432\]](#) [\[46638\]](#) [\[5018\]](#) [\[5044\]](#) [\[5623\]](#) [\[5747\]](#) [\[8102\]](#) (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [\[28341\]](#) [\[46638\]](#) (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [\[46638\]](#)

Belladonna; Opium: (Moderate) Ritonavir is an inhibitor of the cytochrome P450 3A4 isoenzyme and may decrease the metabolism of opium if the two drugs are coadministered. [\[4718\]](#)

Bendroflumethiazide; Nadolol: (Moderate) Cardiac and neurologic events have been reported when ritonavir was concurrently administered with beta-blockers. [\[5044\]](#)

Benzhydrocodone; Acetaminophen: (Moderate) Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen plasma concentrations and subsequent adverse events. Acetaminophen is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[25460\]](#) [\[28100\]](#) [\[58664\]](#) (Moderate) Concurrent use of benzhydrocodone with ritonavir may increase the risk of increased opioid-related adverse reactions, such as fatal respiratory depression. Consider a dose reduction of benzhydrocodone until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. Discontinuation of ritonavir in a patient taking benzhydrocodone may decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to opioid agonists. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Benzhydrocodone is a prodrug for hydrocodone. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and a weak in vitro inhibitor of CYP2D6. [\[47165\]](#) [\[62889\]](#)

Benzphetamine: (Moderate) Warn patients that the risk of amphetamine toxicity may be increased during concurrent use of ritonavir, a strong CYP2D6 inhibitor. Amphetamines are partially metabolized by CYP2D6 and have serotonergic properties; inhibition of amphetamine metabolism may increase the risk of serotonin syndrome or other toxicity. If serotonin syndrome occurs, both the amphetamine and CYP2D6 inhibitor should be discontinued and appropriate medical treatment should be implemented. [\[25887\]](#) [\[29219\]](#) [\[33263\]](#) [\[47165\]](#) [\[57067\]](#)

Bepiridil: (Severe) Ritonavir can produce large increases in plasma concentrations of certain drugs metabolized by cytochrome P450 3A4. The concurrent use of ritonavir is contraindicated with bepridil. [\[46638\]](#) [\[5044\]](#)

Betamethasone: (Moderate) Consider an alternative corticosteroid that is less affected by CYP3A4 (i.e., beclomethasone or prednisolone), particularly for long-term use, in patients receiving ritonavir. Coadministration may significantly increase betamethasone exposure increasing the risk for Cushing's syndrome and adrenal suppression. Ritonavir is a strong CYP3A4 inhibitor and betamethasone is a CYP3A4 substrate. Another strong CYP3A4 inhibitor has been reported to decrease the metabolism of certain corticosteroids by up to 60%. [\[28341\]](#) [\[47165\]](#) [\[63066\]](#)

Betaxolol: (Moderate) Cardiac and neurologic events have been reported when ritonavir was concurrently administered with beta-blockers. [\[5044\]](#)

Betrixaban: (Major) Avoid betrixaban use in patients with severe renal impairment receiving ritonavir. Reduce betrixaban dosage to 80 mg PO once followed by 40 mg PO once daily in all other patients receiving ritonavir. Bleeding risk may be increased; monitor patients closely for signs and symptoms of bleeding. Betrixaban is a substrate of P-gp; ritonavir inhibits P-gp. [28380] [56579] [62037]

Bexarotene: (Major) Avoid the concomitant use of bexarotene and lopinavir; ritonavir as decreased plasma concentrations of lopinavir may occur resulting in reduced therapeutic effect. Consider alternative therapy. Bexarotene is a moderate CYP3A4 inducer and lopinavir is a CYP3A4 substrate. [28341] [61590]

Bicalutamide: (Major) Bicalutamide is metabolized by cytochrome P450 3A4. Substances that are potent inhibitors of CYP3A4 activity, such as protease inhibitors, decrease the metabolism of bicalutamide and increase bicalutamide concentrations. This increase may be clinically relevant as adverse reactions to bicalutamide are related to dose and exposure. [7874]

Bictegravir; Emtricitabine; Tenofovir Alafenamide: (Moderate) Concurrent use of lopinavir with tenofovir alafenamide may result in elevated tenofovir serum concentrations. Tenofovir alafenamide is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. When 10 mg of tenofovir alafenamide was administered daily with lopinavir; ritonavir (800 mg/200 mg PO daily), the tenofovir C_{max} and AUC increased by 2.19-fold and 1.47-fold, respectively. Monitor for increased toxicities if these drugs are given together. [60269] [61510] [61511] [61513]

Bismuth Subcitrate Potassium; Metronidazole; Tetracycline: (Major) Avoid coadministration of lopinavir with metronidazole due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Potential QT prolongation has been reported in limited case reports with metronidazole. Additionally, oral solutions of lopinavir; ritonavir contain ethanol which can produce disulfiram-like reactions when coadministered with metronidazole. [28341] [57377] [57378] [65157] [65170] (Major) Medications with significant alcohol content should not be ingested during therapy with metronidazole and should be avoided for 3 days after therapy is discontinued. Oral solutions of ritonavir contain ethanol. Administration of ritonavir oral solution to patients receiving or who have recently received disulfiram or metronidazole may result in disulfiram-like reactions. A disulfiram reaction would not be expected to occur with non-ethanol containing formulations of ritonavir. [28315] [28581] [47165]

Bismuth Subsalicylate; Metronidazole; Tetracycline: (Major) Avoid coadministration of lopinavir with metronidazole due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Potential QT prolongation has been reported in limited case reports with metronidazole. Additionally, oral solutions of lopinavir; ritonavir contain ethanol which can produce disulfiram-like reactions when coadministered with metronidazole. [28341] [57377] [57378] [65157] [65170] (Major) Medications with significant alcohol content should not be ingested during therapy with metronidazole and should be avoided for 3 days after therapy is discontinued. Oral solutions of ritonavir contain ethanol. Administration of ritonavir oral solution to patients receiving or who have recently received disulfiram or metronidazole may result in disulfiram-like reactions. A disulfiram reaction would not be expected to occur with non-ethanol containing formulations of ritonavir. [28315] [28581] [47165]

Bisoprolol: (Moderate) Cardiac and neurologic events have been reported when ritonavir was concurrently administered with beta-blockers. [5044]

Bisoprolol; Hydrochlorothiazide, HCTZ: (Moderate) Cardiac and neurologic events have been reported when ritonavir was concurrently administered with beta-blockers. [5044]

Boceprevir: (Major) Concurrent administration of lopinavir; ritonavir with boceprevir is not recommended due to the potential for HIV and hepatitis C treatment failures. Use of this combination has resulted in decreased serum concentrations of both drugs. Lopinavir; ritonavir is an inhibitor, inducer, and substrate of CYP3A4; boceprevir is an inhibitor and substrate of this isoenzyme. Additionally, both are substrates and inhibitors of the drug efflux transporter P-glycoprotein (P-gp). If these drugs are coadministered, health care providers are advised to closely monitor for decreased treatment response and virologic rebound. Health care providers are also encouraged to report any drug-related adverse reactions to the FDA MedWatch Program. [28341] [44314] [48674] [51080] (Major) Concurrent administration of ritonavir with boceprevir is not recommended due to the potential for HIV and hepatitis C treatment failures. This combination has resulted in decreased serum concentrations of both medications. Ritonavir is an inhibitor, inducer, and substrate of the hepatic isoenzyme CYP3A4; boceprevir is an inhibitor and substrate of this isoenzyme. Additionally, both drugs are substrates and inhibitors of the drug efflux transporter P-glycoprotein (PGP). If these drugs are coadministered, health care providers are advised to closely monitor for decreased treatment response and virologic rebound. Health care providers are also encouraged to report any drug-related adverse reactions to the FDA MedWatch Program. [28315] [44314] [48674]

Bortezomib: (Moderate) In vitro studies with human liver microsomes indicate that bortezomib is a significant substrate for CYP3A4. Agents that inhibit CYP3A4, such as ritonavir, may increase the exposure to bortezomib and increase the risk for toxicity. The manufacturer warns that patients who are receiving bortezomib concurrently with potent CYP3A4 inhibitors should be closely monitored for potential toxicity. Additionally, ritonavir can cause peripheral neuropathy. It may be prudent to monitor patients for signs and symptoms of neuropathy. [28383]

Bosentan: (Major) Do not administer bosentan with anti-retroviral protease inhibitors that are not boosted with ritonavir as decreased protease inhibitor concentrations are expected. In addition, administration of anti-retroviral protease inhibitors with bosentan may increase bosentan serum concentrations due to the inhibition of the CYP3A4 isoenzyme. In patients who have been receiving protease inhibitor therapy for at least 10 days, initiate bosentan at the recommended initial dose once daily or every other day based on tolerability. For patients on bosentan who need protease inhibitor therapy, discontinue use of bosentan at least 36 hours prior to starting protease inhibitor therapy. After 10 days of the protease inhibitor therapy, bosentan may be restarted at the recommended initial dose once daily or every other day based on tolerability. Bosentan is a substrate for organic anion transport protein (OATP), CYP3A, and CYP2C9. In healthy subjects, initial and steady state trough plasma concentrations of bosentan were approximately 48-fold and 5-fold higher, respectively, after coadministration of bosentan 125 mg twice daily PO and lopinavir; ritonavir 400/100 mg twice daily PO compared to those measured after bosentan alone. This is most likely explained by inhibition by lopinavir of OATP-mediated uptake into hepatocytes;

toxicity of bosentan is possible. Monitor for potential adverse effects of bosentan during coadministration with CYP2C9 or CYP3A4 inhibitors; excessive bosentan dosage may result in hypotension or elevated hepatic enzyme. Additionally, bosentan is a significant inducer of CYP3A4 and CYP2C9 hepatic enzymes. Theoretically, bosentan may increase the clearance of the protease inhibitors and potentially lead to a reduction of anti-retroviral efficacy. However, this interaction has not been studied. [28142] [28315] [28341] [28496] [28731] [28839] [28995] [29012] [31320] [32432] [46638] [56579] [61510] [61511] [61512] [61513]

Bosutinib: (Major) Avoid concomitant use of bosutinib and ritonavir or lopinavir; ritonavir as bosutinib plasma exposure may be significantly increased resulting in an increased risk of bosutinib adverse events (e.g., myelosuppression, GI toxicity). Bosutinib is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. In a cross-over trial in 24 healthy volunteers, the C_{max} and AUC values of bosutinib were increased 5.2-fold and 8.6-fold, respectively, when a single oral dose of bosutinib 100 mg PO was administered after 5 days of a strong CYP3A4 inhibitor. [28315] [51739]

Brentuximab vedotin: (Minor) Concomitant administration of brentuximab vedotin and ritonavir may increase the exposure of monomethyl auristatin E (MMAE), one of the 3 components released from brentuximab vedotin. The manufacturer suggests that potent CYP3A4 inhibitors, such as ritonavir, may alter MMAE exposure as MMAE is a CYP3A4 substrate. Monitor patients for adverse reactions. [11416] [45378] [5044] [5110]

Brexpiprazole: (Major) Because brexpiprazole is primarily metabolized by CYP3A4 and CYP2D6, the manufacturer recommends that the brexpiprazole dose be reduced to one-quarter (25%) of the usual dose in patients receiving a moderate to strong inhibitor of CYP3A4 inhibitor in combination with a moderate to strong inhibitor of CYP2D6. Ritonavir (including lopinavir; ritonavir) is a strong inhibitor of CYP3A4 and a moderate inhibitor of CYP2D6. If these agents are used in combination, the patient should be carefully monitored for brexpiprazole-related adverse reactions. If the co-administered CYP inhibitor is discontinued, adjust the brexpiprazole dose to its original level. [59949]

Brigatinib: (Major) Avoid coadministration of brigatinib with ritonavir if possible due to increased plasma exposure of brigatinib; an increase in brigatinib-related adverse reactions may occur. If concomitant use is unavoidable, reduce the dose of brigatinib by approximately 50% without breaking tablets (i.e., from 180 mg to 90 mg; from 90 mg to 60 mg); after discontinuation of ritonavir, resume the brigatinib dose that was tolerated prior to initiation of ritonavir. Brigatinib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased the AUC and C_{max} of brigatinib by 101% and 21%, respectively. [28315] [61909]

Brimonidine; Timolol: (Moderate) Timolol is significantly metabolized by CYP2D6 isoenzymes. CYP2D6 inhibitors, such as ritonavir, may impair timolol metabolism; the clinical significance of such interactions is unknown. [5044] [5270]

Bromocriptine: (Major) When bromocriptine is used for diabetes, avoid coadministration with ritonavir ensuring adequate washout before initiating bromocriptine. Use this combination with caution in patients receiving bromocriptine for other indications. Concurrent use may significantly increase bromocriptine concentrations. Bromocriptine is extensively metabolized in the liver via CYP3A4; ritonavir is a strong inhibitor of CYP3A4. [28337] [35591] [47165]

Brompheniramine; Guaifenesin; Hydrocodone: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531]

Brompheniramine; Hydrocodone; Pseudoephedrine: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531]

Budesonide: (Major) Avoid coadministration of oral budesonide and ritonavir due to the potential for increased budesonide exposure. Use caution with inhaled forms of budesonide as systemic exposure to the corticosteroid may also increase. Budesonide is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. In the presence of another strong CYP3A4 inhibitor, the systemic exposure to oral budesonide was increased by 8-fold. [28315] [31824] [34979] [47165] (Major) Decreased lopinavir plasma concentrations have been observed when systemic budesonide and lopinavir; ritonavir are coadministered, increasing the risk for HIV treatment failure. Additionally, inhibition of CYP3A4 by lopinavir; ritonavir increases plasma exposure of budesonide, resulting in significantly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving inhaled or intranasally administered budesonide with ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of budesonide (or budesonide-containing products) and ritonavir (or ritonavir-containing products or treatment regimens) is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. If concurrent use if required, caution and carefully monitor of HIV treatment status and adverse effects are recommended. [28341] [31824] [34979] [51080]

Budesonide; Formoterol: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more

clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28318] [28341] [32901] [33925] [41231] [65157] [65170] (Major) Avoid coadministration of oral budesonide and ritonavir due to the potential for increased budesonide exposure. Use caution with inhaled forms of budesonide as systemic exposure to the corticosteroid may also increase. Budesonide is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. In the presence of another strong CYP3A4 inhibitor, the systemic exposure to oral budesonide was increased by 8-fold. [28315] [31824] [34979] [47165] (Major) Decreased lopinavir plasma concentrations have been observed when systemic budesonide and lopinavir; ritonavir are coadministered, increasing the risk for HIV treatment failure. Additionally, inhibition of CYP3A4 by lopinavir; ritonavir increases plasma exposure of budesonide, resulting in significantly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving inhaled or intranasally administered budesonide with ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of budesonide (or budesonide-containing products) and ritonavir (or ritonavir-containing products or treatment regimens) is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. If concurrent use is required, caution and carefully monitor of HIV treatment status and adverse effects are recommended. [28341] [31824] [34979] [51080]

Bupivacaine Liposomal: (Minor) Bupivacaine is metabolized by cytochrome P450 (CYP) 3A4 isoenzymes. Known inhibitors of CYP 3A4, such as anti-retroviral protease inhibitors, may result in increased systemic levels of bupivacaine when given concurrently, with potential for toxicity. Although not studied, dosage adjustments of bupivacaine may be needed. [4718]

Bupivacaine: (Minor) Bupivacaine is metabolized by cytochrome P450 (CYP) 3A4 isoenzymes. Known inhibitors of CYP 3A4, such as anti-retroviral protease inhibitors, may result in increased systemic levels of bupivacaine when given concurrently, with potential for toxicity. Although not studied, dosage adjustments of bupivacaine may be needed. [4718]

Bupivacaine; Lidocaine: (Moderate) Anti-retroviral protease inhibitors can inhibit hepatic cytochrome P450 3A4, an isoenzyme that is partially responsible for the metabolism of lidocaine. The concurrent use of systemic lidocaine and anti-retroviral protease inhibitors should be carefully monitored due to the potential for serious toxicity. [4718] [5172] (Minor) Bupivacaine is metabolized by cytochrome P450 (CYP) 3A4 isoenzymes. Known inhibitors of CYP 3A4, such as anti-retroviral protease inhibitors, may result in increased systemic levels of bupivacaine when given concurrently, with potential for toxicity. Although not studied, dosage adjustments of bupivacaine may be needed. [4718]

Buprenorphine: (Major) Avoid coadministration of lopinavir with buprenorphine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Buprenorphine has been associated with QT prolongation and has a possible risk of torsade de pointes (TdP). [28341] [41235] [41666] [60270] [65157] [65170] (Moderate) Concomitant use of buprenorphine and ritonavir can increase the plasma concentration of buprenorphine, resulting in increased or prolonged opioid effects, particularly when ritonavir is added after a stable buprenorphine dose is achieved. If concurrent use is necessary, consider dosage reduction of buprenorphine until stable drug effects are achieved. Monitor patient for respiratory depression and sedation at frequent intervals. When stopping ritonavir, the buprenorphine concentration will decrease, potentially resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependency. If ritonavir is discontinued, consider increasing buprenorphine dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. Buprenorphine is a substrate of CYP3A4. ritonavir is a strong CYP3A4 inhibitor. [41235] [41666] [47165]

Buprenorphine; Naloxone: (Major) Avoid coadministration of lopinavir with buprenorphine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Buprenorphine has been associated with QT prolongation and has a possible risk of torsade de pointes (TdP). [28341] [41235] [41666] [60270] [65157] [65170] (Moderate) Concomitant use of buprenorphine and ritonavir can increase the plasma concentration of buprenorphine, resulting in increased or prolonged opioid effects, particularly when ritonavir is added after a stable buprenorphine dose is achieved. If concurrent use is necessary, consider dosage reduction of buprenorphine until stable drug effects are achieved. Monitor patient for respiratory depression and sedation at frequent intervals. When stopping ritonavir, the buprenorphine concentration will decrease, potentially resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependency. If ritonavir is discontinued, consider increasing buprenorphine dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. Buprenorphine is a substrate of CYP3A4. ritonavir is a strong CYP3A4 inhibitor. [41235] [41666] [47165]

Bupropion: (Moderate) Concurrent administration of bupropion with ritonavir results in decreased concentrations of bupropion and its active metabolite. According to the manufacturers of bupropion, increased doses of bupropion may be necessary during concurrent therapy; however, the maximum recommended dose of bupropion should not be exceeded. Closely monitor bupropion efficacy if these drugs are given together. Ritonavir induces CYP2B6, which is responsible for bupropion's metabolism. In one study, ritonavir 100 mg twice daily reduced the AUC and Cmax of bupropion by 22% and 21%, respectively. In addition, exposure to the active metabolite of bupropion (hydroxybupropion) was decreased by 23%. When given with ritonavir 600 mg twice daily, the AUC and Cmax of bupropion decreased by 66% and 63% respectively and exposure to hydroxybupropion decreased by 78%. [28058] [28315] [34743] [34744] [34745] [34746] [44095]

Bupropion; Naltrexone: (Moderate) Concurrent administration of bupropion with ritonavir results in decreased concentrations of bupropion and its active metabolite. According to the manufacturers of bupropion, increased doses of bupropion may be necessary during concurrent therapy; however, the maximum recommended dose of bupropion should not be exceeded. Closely monitor bupropion efficacy if these drugs are given together. Ritonavir induces CYP2B6, which is responsible for bupropion's metabolism. In one study, ritonavir 100 mg twice daily reduced the AUC and Cmax of bupropion by 22% and 21%, respectively. In addition, exposure to the active metabolite of bupropion (hydroxybupropion) was decreased by 23%. When given with ritonavir 600 mg twice daily, the AUC and Cmax of bupropion decreased by 66% and 63% respectively and exposure to hydroxybupropion decreased by 78%. [28058] [28315] [34743] [34744] [34745] [34746] [44095]

Buspirone: (Major) When buspirone is administered with a potent inhibitor of CYP3A4 like ritonavir, a low dose of buspirone used cautiously is recommended. Some patients receiving drugs that are potent inhibitors of CYP3A4 with buspirone have reported lightheadedness, asthenia, dizziness, and drowsiness. If the two drugs are to be used in combination, a low dose of buspirone (e.g., 2.5 mg

PO twice daily) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment. Several other anti-retroviral protease inhibitors also inhibit CYP3A4, and these may interact with buspirone in a similar manner. [\[28001\]](#) [\[28501\]](#)

Butabarbital: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [\[28341\]](#) [\[46638\]](#) (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [\[46638\]](#)

Cabazitaxel: (Major) Avoid coadministration of cabazitaxel with ritonavir if possible due to increased cabazitaxel exposure. If concomitant use is unavoidable, consider reducing the dose of cabazitaxel by 25%. Cabazitaxel is primarily metabolized by CYP3A4 and ritonavir is a strong CYP3A4 inhibitor. In a drug interaction study, coadministration with another strong CYP3A4 inhibitor increased cabazitaxel exposure by 25%. [\[40981\]](#) [\[47165\]](#)

Cabozantinib: (Major) Avoid coadministration of cabozantinib with ritonavir due to the risk of increased cabozantinib exposure. If concomitant use is unavoidable, reduce the dose of cabozantinib. For patients taking cabozantinib tablets, reduce the dose of cabozantinib by 20 mg (e.g., 60 mg/day to 40 mg/day; 40 mg/day to 20 mg/day); for patients taking cabozantinib capsules, reduce the dose of cabozantinib by 40 mg (e.g., 140 mg/day to 100 mg/day or 100 mg/day to 60 mg/day). Resume the cabozantinib dose that was used prior to initiating treatment with ritonavir 2 to 3 days after discontinuation of ritonavir. Cabozantinib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased single-dose cabozantinib exposure by 38%. Cabozantinib is also P-glycoprotein (P-gp) inhibitor and has the potential to increase plasma concentrations of P-gp substrates such as ritonavir; however, the clinical relevance of this finding is unknown. [\[34557\]](#) [\[52506\]](#) [\[60738\]](#)

Caffeine; Ergotamine: (Severe) Coadministration of ergot alkaloids with potent inhibitors of CYP3A4, like anti-retroviral protease inhibitors is considered contraindicated due to the risk of acute ergot toxicity (e.g., vasospasm leading to cerebral ischemia, peripheral ischemia and/or other serious effects). Several case reports have established the clinical significance of this interaction in the medical literature. In some cases, fatal interactions have occurred. [\[28142\]](#) [\[28341\]](#) [\[28731\]](#) [\[28839\]](#) [\[28995\]](#) [\[32432\]](#) [\[46638\]](#) [\[5018\]](#) [\[5044\]](#) [\[5623\]](#) [\[5747\]](#) [\[8102\]](#)

Calcifediol: (Moderate) Dose adjustment of calcifediol may be necessary during coadministration with ritonavir. Additionally, serum 25-hydroxyvitamin D, intact PTH, and calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with ritonavir. Ritonavir, which is a cytochrome P450 inhibitor, may inhibit enzymes involved in vitamin D metabolism (CYP24A1 and CYP27B1) and may alter serum concentrations of calcifediol. [\[60895\]](#)

Canagliflozin: (Moderate) Monitor for decreased efficacy of canagliflozin if coadministration with ritonavir is necessary. In patients taking ritonavir who have an eGFR greater than 60 mL/min/1.73 m², and are currently tolerating a canagliflozin dose of 100 mg once daily, increase the dose of canagliflozin to 200 mg (taken as two 100 mg tablets) once daily. In patients who are tolerating canagliflozin to 200 mg and who require additional glycemic control, the dose may be increased to 300 mg once daily. In patients taking ritonavir who have an eGFR less than 60 mL/min/1.73 m², and are currently tolerating a canagliflozin dose of 100 mg once daily, increase the dose of canagliflozin to 200 mg (taken as two 100 mg tablets) once daily. Consider other antihyperglycemic therapy in patients who require additional glycemic control. Canagliflozin is a UGT1A9 and 2B4 substrate and ritonavir is a UGT inducer. Coadministration with a nonselective inducer of several UGT enzymes decreased canagliflozin exposure by 51%. In addition, new onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of antiretroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [\[30575\]](#) [\[47165\]](#) [\[53972\]](#) (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors, such as lopinavir. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [\[28341\]](#) [\[30575\]](#)

Canagliflozin; Metformin: (Moderate) Monitor for decreased efficacy of canagliflozin if coadministration with ritonavir is necessary. In patients taking ritonavir who have an eGFR greater than 60 mL/min/1.73 m², and are currently tolerating a canagliflozin dose of 100 mg once daily, increase the dose of canagliflozin to 200 mg (taken as two 100 mg tablets) once daily. In patients who are tolerating canagliflozin to 200 mg and who require additional glycemic control, the dose may be increased to 300 mg once daily. In patients taking ritonavir who have an eGFR less than 60 mL/min/1.73 m², and are currently tolerating a canagliflozin dose of 100 mg once daily, increase the dose of canagliflozin to 200 mg (taken as two 100 mg tablets) once daily. Consider other antihyperglycemic therapy in patients who require additional glycemic control. Canagliflozin is a UGT1A9 and 2B4 substrate and ritonavir is a UGT inducer. Coadministration with a nonselective inducer of several UGT enzymes decreased canagliflozin exposure by 51%. In addition, new onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of antiretroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [\[30575\]](#) [\[47165\]](#) [\[53972\]](#) (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors, such as lopinavir. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy.

Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [28341] [30575] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Cannabidiol: (Moderate) Consider a dose adjustment of cannabidiol if coadministered with ritonavir. Coadministration may alter cannabidiol plasma concentrations increasing the risk of adverse reactions or decreasing efficacy. Cannabidiol is metabolized by CYP3A4 and CYP2C19; ritonavir is a strong inhibitor of CYP3A4 and a strong inducer of CYP2C19. [47165] [56579] [63309]

Carbamazepine: (Major) Concurrent administration of lopinavir; ritonavir (Kaletra) twice daily with carbamazepine should be done cautiously. Once daily lopinavir; ritonavir should not be administered with carbamazepine due to hepatic enzyme induction by the antiepileptic. While the use of ritonavir as a single PI has been noted to induce anticonvulsant metabolism, coadministration of lopinavir; ritonavir (Kaletra) with carbamazepine will more likely result in decreased lopinavir plasma concentrations, leading to loss of virologic control. In addition, coadministration may result in increased carbamazepine concentrations; carbamazepine is a CYP3A4 substrate and lopinavir; ritonavir is a potent CYP3A4 inhibitor. If lopinavir; ritonavir (Kaletra) is used with carbamazepine, the patient's HIV status, as well as carbamazepine plasma concentrations, should be closely monitored. [28341] [41237] [46638] (Major) Ritonavir decreases the hepatic CYP metabolism of carbamazepine, resulting in increased carbamazepine concentrations. In addition, carbamazepine increases the metabolism of the protease inhibitors and may lead to decreased efficacy of these medications. Carbamazepine is a potent inducer and substrate of the hepatic isoenzyme CYP3A4; ritonavir is a substrate and inhibitor of this isoenzyme. In addition, carbamazepine induces P-glycoprotein (P-gp), a drug efflux transporter for which ritonavir is a substrate. Treatment failures have been reported with protease inhibitors when carbamazepine is used concomitantly. The appropriate drug-dose adjustments necessary to ensure optimum levels of both antiretroviral drugs and carbamazepine are unknown. If used concomitantly, the patient should be observed for changes in the clinical efficacy of the antiretroviral regimen or for carbamazepine toxicity. [28315] [46638]

Carbetapentane; Chlorpheniramine: (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [34390] [47165] [57935] [58664]

Carbetapentane; Chlorpheniramine; Phenylephrine: (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [34390] [47165] [57935] [58664]

Carbetapentane; Diphenhydramine; Phenylephrine: (Moderate) Concurrent administration of diphenhydramine with ritonavir may result in elevated plasma concentrations of diphenhydramine. Diphenhydramine is a CYP2D6 substrate, and ritonavir is a CYP2D6 inhibitor. Caution and close monitoring are advised if these drugs are administered together. [34522] [34523] [47165] [58664]

Carbinoxamine; Hydrocodone; Phenylephrine: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531]

Carbinoxamine; Hydrocodone; Pseudoephedrine: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531]

Cariprazine: (Major) Cariprazine and its active metabolites are extensively metabolized by CYP3A4. When a strong CYP3A4 inhibitor, such as ritonavir, is initiated in a patient who is on a stable dose of cariprazine, reduce the cariprazine dosage by half. For adult patients taking cariprazine 4.5 mg daily, the dosage should be reduced to 1.5 mg or 3 mg daily. For patients taking cariprazine 1.5 mg daily, the dosing frequency should be adjusted to every other day. When the CYP3A4 inhibitor is withdrawn, the cariprazine dosage may need to be increased. When initiating cariprazine in a patient who is stable on a strong CYP3A4 inhibitor, the patient should be administered 1.5 mg of cariprazine on Day 1 and on Day 3 with no dose administered on Day 2. From Day 4 onward, the dose should be administered at 1.5 mg daily, then increased to a maximum dose of 3 mg daily. When the CYP3A4 inhibitor is withdrawn, the cariprazine dosage may need to be increased. [28341] [60164]

Carteolol: (Moderate) Cardiac and neurologic events have been reported when ritonavir was concurrently administered with beta-blockers. [5044]

Carvedilol: (Moderate) Inhibitors of the hepatic CYP450 isozyme CYP2D6, such as ritonavir, may inhibit the hepatic oxidative metabolism of carvedilol. In addition, both drugs are inhibitors and substrates for P-glycoprotein (P-gp). Close monitoring of serum drug concentrations and/or therapeutic and adverse effects is required when carvedilol is coadministered with ritonavir. [4718] [5044] [5267]

Ceritinib: (Major) Avoid coadministration of ceritinib with ritonavir due to increased exposure to ceritinib; plasma concentrations of ritonavir may also increase. If concomitant use is unavoidable, decrease the dose of ceritinib by approximately one-third, rounded to the nearest multiple of 150 mg; monitor for treatment-related adverse reactions. After ritonavir is discontinued, resume the dose of ceritinib taken prior to initiating ritonavir. Both drugs are CYP3A4 substrates and strong CYP3A4 inhibitors. Coadministration with another strong CYP3A4 inhibitor increased ceritinib exposure by 2.9-fold after a single dose in healthy subjects. [47165] [57094] (Major) Avoid coadministration of lopinavir with ceritinib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Interrupt, dose reduce, or discontinue ceritinib if QT prolongation occurs. Ceritinib causes concentration-dependent QT prolongation. Lopinavir is also associated with QT prolongation. [28341] [56579] [57094] [65157] [65170]

Cetirizine: (Moderate) Coadministration of cetirizine and ritonavir resulted in a 42% increase in the AUC, 53% increase in half-life, and 29% decrease in clearance of cetirizine. Cetirizine did not alter ritonavir disposition. [28874] [33350]

Cetirizine; Pseudoephedrine: (Moderate) Coadministration of cetirizine and ritonavir resulted in a 42% increase in the AUC, 53% increase in half-life, and 29% decrease in clearance of cetirizine. Cetirizine did not alter ritonavir disposition. [28874] [33350]

Cevimeline: (Major) Cevimeline is metabolized by CYP3A4 and CYP2D6. Anti-retroviral protease inhibitors inhibit one or both of these isoenzymes and are expected to lead to an increase in cevimeline plasma concentrations. [28001] [34711] [48617]

Chloramphenicol: (Moderate) Concurrent administration of chloramphenicol with ritonavir may result in elevated plasma concentrations of ritonavir, and subsequent adverse events. Chloramphenicol is an inhibitor of the hepatic isoenzyme CYP3A4; ritonavir is a substrate of this enzyme. Monitor patient for ritonavir-related adverse events. [29624] [58664]

Chlordiazepoxide: (Major) CYP3A4 inhibitors, such as protease inhibitors, may reduce the metabolism of chlordiazepoxide and increase the potential for benzodiazepine toxicity. A decrease in the chlordiazepoxide dose may be needed. [32432] [5286]

Chlordiazepoxide; Clidinium: (Major) CYP3A4 inhibitors, such as protease inhibitors, may reduce the metabolism of chlordiazepoxide and increase the potential for benzodiazepine toxicity. A decrease in the chlordiazepoxide dose may be needed. [32432] [5286]

Chloroquine: (Major) Avoid coadministration of chloroquine and lopinavir due the risk of additive QT prolongation. If use together is necessary, obtain an ECG at baseline to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Chloroquine is associated with an increased risk of QT prolongation and torsade de pointes (TdP); fatalities have been reported. The risk of QT prolongation is increased with higher chloroquine doses. Lopinavir is also associated with QT prolongation. [28229] [28230] [28231] [28341] [29758] [65157] [65170]

Chlorpheniramine: (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [34390] [47165] [57935] [58664]

Chlorpheniramine; Codeine: (Moderate) Concomitant use of codeine with ritonavir may alter codeine plasma concentrations, resulting in an unpredictable effect such as reduced efficacy or symptoms of opioid withdrawal or prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage adjustment of codeine until stable drug effects are achieved. Discontinuation of ritonavir could alter codeine plasma concentrations, resulting in an unpredictable effect such as prolonged opioid adverse reactions or decreased opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to codeine. If ritonavir is discontinued, monitor the patient carefully and consider adjusting the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Ritonavir is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. CYP3A4 inhibitors may increase codeine-related adverse effects while CYP2D6 inhibitors may reduce efficacy. [33654] [34883] [47165] (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [34390] [47165] [57935] [58664]

Chlorpheniramine; Dextromethorphan: (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [34390] [47165] [57935] [58664]

Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [34390] [47165] [57935] [58664]

Chlorpheniramine; Dihydrocodeine; Phenylephrine: (Moderate) Concomitant use of dihydrocodeine with ritonavir may increase dihydrocodeine plasma concentrations, resulting in greater metabolism by CYP2D6, increased dihydromorphine concentrations, and prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of dihydrocodeine until stable drug effects are achieved. Discontinuation of ritonavir could decrease dihydrocodeine plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to dihydrocodeine. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Ritonavir is a strong inhibitor of CYP3A4, an isoenzyme partially responsible for the metabolism of dihydrocodeine. [30282] [47165] (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [34390] [47165] [57935] [58664]

Chlorpheniramine; Dihydrocodeine; Pseudoephedrine: (Moderate) Concomitant use of dihydrocodeine with ritonavir may increase dihydrocodeine plasma concentrations, resulting in greater metabolism by CYP2D6, increased dihydromorphine concentrations, and prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of dihydrocodeine until stable drug effects are achieved. Discontinuation of ritonavir could decrease dihydrocodeine plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to dihydrocodeine. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Ritonavir is a strong inhibitor of CYP3A4, an isoenzyme partially responsible for the metabolism of dihydrocodeine. [30282] [47165] (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [34390] [47165] [57935] [58664]

Chlorpheniramine; Guaifenesin; Hydrocodone; Pseudoephedrine: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531] (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [34390] [47165] [57935] [58664]

Chlorpheniramine; Hydrocodone: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531] (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [34390] [47165] [57935] [58664]

Chlorpheniramine; Hydrocodone; Phenylephrine: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531] (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [34390] [47165] [57935] [58664]

Chlorpheniramine; Hydrocodone; Pseudoephedrine: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531] (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [34390] [47165] [57935] [58664]

Chlorpheniramine; Phenylephrine: (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [34390] [47165] [57935] [58664]

Chlorpheniramine; Pseudoephedrine: (Moderate) Concurrent administration of chlorpheniramine with ritonavir may result in elevated plasma concentrations of chlorpheniramine. Chlorpheniramine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Monitor for adverse effects if these drugs are administered together. [34390] [47165] [57935] [58664]

Chlorpromazine: (Major) Avoid coadministration of lopinavir with chlorpromazine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Chlorpromazine, a phenothiazine, is associated with an established risk of QT prolongation and torsade de pointes (TdP). [28341] [28417] [43065] [65157] [65170]

Ciclesonide: (Moderate) Coadministration of ciclesonide with ritonavir may cause elevated ciclesonide serum concentrations, potentially resulting in Cushing's syndrome and adrenal suppression. Ciclesonide is a CYP3A4 substrate; ritonavir is a strong inhibitor of CYP3A4. Corticosteroids, such as beclomethasone and prednisolone, whose concentrations are less affected by strong CYP3A4 inhibitors, should be considered, especially for long-term use. [28341] [47165]

Cidofovir: (Moderate) Additive adverse effects may be seen when cidofovir is given with other agents that cause neutropenia. Patients receiving anti-retroviral protease inhibitors in combination with cidofovir may have an increased risk of iritis or uveitis. [24859]

Cilostazol: (Major) Concurrent administration of cilostazol with protease inhibitors can result in elevated cilostazol plasma concentrations; the manufacturer recommends prescribers consider up to a 50% reduction in cilostazol dosage during concurrent administration. Cilostazol is metabolized by the hepatic isoenzyme CYP3A4; protease inhibitors block this enzyme. Caution and close monitoring are advised if these drugs are administered together. [47165] [48620]

Cimetidine: (Moderate) Concurrent administration of cimetidine with ritonavir may result in elevated plasma concentrations of ritonavir. Cimetidine is an inhibitor of the hepatic isoenzymes CYP3A4 and CYP2D6; ritonavir is partially metabolized by both of these enzymes. Monitor for adverse events if these drugs are administered together. [34364] [56579] [57012] [58664]

Cinacalcet: (Moderate) Concurrent administration of cinacalcet with ritonavir may result in elevated plasma concentrations of cinacalcet. Cinacalcet is a substrate of CYP3A4; ritonavir is a potent inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [47165] [58664]

Ciprofloxacin: (Major) Avoid coadministration of lopinavir with ciprofloxacin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Rare cases of QT prolongation and torsade de pointes (TdP) have been reported with ciprofloxacin during postmarketing surveillance. [28341] [43411] [65157] [65170]

Cisapride: (Severe) Concurrent use of cisapride with anti-retroviral protease inhibitors (PI) is contraindicated due to the risk of life threatening cardiac arrhythmias such as torsade de pointes (TdP). Cisapride is metabolized by CYP3A4, and all PIs inhibit this enzyme; thus, coadministration may increase cisapride plasma concentrations and increase the risk of adverse events. Cases of QT prolongation and ventricular arrhythmias, including TdP and death, have been observed during post-marketing surveillance when cisapride is administered with potent CYP3A4 inhibitors. [28978] [28995] [46638] [47221]

Citalopram: (Major) Avoid coadministration of lopinavir with citalopram due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Citalopram causes dose-dependent QT interval prolongation. [28269] [28341] [65157] [65170] (Minor) Concurrent use of ritonavir may increase citalopram exposure and treatment-related adverse effects. Ritonavir is a strong CYP3A4 inhibitor. Because CYP3A4 is one of the primary enzymes involved in the metabolism of citalopram, it is expected that strong CYP3A4 inhibitors might decrease the clearance of citalopram. However, coadministration of citalopram and another strong CYP3A4 inhibitor ketoconazole did not significantly affect the pharmacokinetics of citalopram. [28269] [47165]

Clarithromycin: (Major) Avoid coadministration of lopinavir with clarithromycin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Clarithromycin is associated with an established risk for QT prolongation and torsade de pointes (TdP). [28225] [28238] [28341] [28413] [28419] [65157] [65170] (Major) Because the exposure to 14-OH clarithromycin is significantly decreased by ritonavir, consider alternative antibiotic therapy for indications other than *Mycobacterium avium*. Clarithromycin doses above 1000 mg should not be administered with ritonavir. If coadministration cannot be avoided, clarithromycin dosage reductions are recommended in patients with renal impairment (CrCl 30 to 60 mL/minute, decrease clarithromycin by 50%; CrCl less than 30 mL/minute, decrease clarithromycin by 75%). Concomitant administration of ritonavir and clarithromycin resulted in a 77% increase in clarithromycin exposure and a 100% decrease in 14-OH clarithromycin exposure. The microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria. [28238] [46638] [47165]

Clevidipine: (Moderate) Ritonavir is expected to decrease the hepatic CYP metabolism of calcium-channel blockers (mainly through CYP3A4 inhibition) resulting in increased calcium-channel blocker concentrations. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [5044]

Clindamycin: (Moderate) Monitor for an increase in clindamycin-related adverse reactions with coadministration of ritonavir as concurrent use may increase clindamycin exposure. Clindamycin is a CYP3A4 substrate; ritonavir is a strong inhibitor of CYP3A4. [44982] [47165]

Clobazam: (Moderate) Monitor for decreased response to lopinavir; ritonavir and increased adverse effects from clobazam and lopinavir; ritonavir during concurrent use. Coadministration may result in elevated plasma concentrations of clobazam and altered concentrations of lopinavir and ritonavir. Clobazam is a substrate of CYP3A4, weak inducer of CYP3A4, and a weak inhibitor of CYP2D6. Ritonavir is a substrate of CYP3A4 and CYP2D6. Ritonavir is also a potent inhibitor of CYP3A4. Lopinavir is a substrate of CYP3A4. [28341] [46370] [56579] (Moderate) Monitor for reduced response to ritonavir and increased adverse effects from both clobazam and ritonavir during concurrent use. Coadministration may result in elevated plasma concentrations of clobazam and altered concentrations of ritonavir. Clobazam is a substrate of CYP3A4, weak inducer of CYP3A4, and an inhibitor of CYP2D6. Ritonavir is a substrate of CYP3A4 and CYP2D6. Ritonavir is also a strong inhibitor of CYP3A4. [46370] [47165]

Clofarabine: (Moderate) Concomitant use of clofarabine, a substrate of OCT1, and ritonavir, an inhibitor of OCT1, may result in increased clofarabine levels. Therefore, monitor for signs of clofarabine toxicity such as gastrointestinal toxicity (e.g., nausea, vomiting,

diarrhea, mucosal inflammation), hematologic toxicity, and skin toxicity (e.g. hand and foot syndrome, rash, pruritus) in patients also receiving OCT1 inhibitors. [51834] [54578]

Clofazimine: (Major) Avoid coadministration of lopinavir with clofazimine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. QT prolongation and torsade de pointes (TdP) have been reported in patients receiving clofazimine in combination with QT prolonging medications. [28341] [63936] [65157] [65170]

Clomipramine: (Moderate) A dose reduction of the tricyclic antidepressant (TCA) may be necessary when coadministered with ritonavir. Concurrent use may result in elevated TCA plasma concentrations. [47165]

Clonazepam: (Moderate) Use protease inhibitors cautiously and carefully monitor patients receiving concurrent clonazepam due to impaired metabolism of clonazepam leading to exaggerated concentrations and adverse effects, such as CNS and/or respiratory depression. Clonazepam is a CYP3A4 substrate. Protease inhibitors are CYP3A4 inhibitors. [28315] [28444] [32432]

Clopidogrel: (Major) Avoid coadministration of clopidogrel with ritonavir due to the potential for decreased clopidogrel efficacy. Prasugrel is preferred to clopidogrel if coadministration with ritonavir is necessary. Although clopidogrel is primarily converted to its active metabolite via CYP2C19, it has been suggested that inhibition of CYP3A4 also reduces its conversion to the active metabolite, thereby reducing its antiplatelet effect. Ritonavir is a strong CYP3A4 inhibitor. [28315] [65211] [65250]

Clorazepate: (Major) CYP3A4 inhibitors, such as protease inhibitors, may reduce the metabolism of N-desmethyldiazepam, the active metabolite of clorazepate, and increase the potential for benzodiazepine toxicity. Monitor patients closely who receive concurrent therapy. [46638] [4718] [5074]

Clozapine: (Major) Avoid coadministration of lopinavir with clozapine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Treatment with clozapine has been associated with QT prolongation, torsade de pointes (TdP), cardiac arrest, and sudden death. [28262] [28341] [28416] [5044] [65157] [65170] (Major) Consider a clozapine dose adjustment if coadministered with ritonavir and monitor for efficacy and adverse reactions. If ritonavir is discontinued, monitor for lack of clozapine effect and adverse effects and adjust dose if necessary. A clinically relevant increase or decrease in the plasma concentration of clozapine may occur during concurrent use. Clozapine is partially metabolized by CYP3A4, CYP2D6, and CYP1A2. Ritonavir is a strong CYP3A4 and weak CYP2D6 inhibitor and a moderate inducer of CYP1A2. [28262] [47165] [56579]

Cobicistat: (Severe) Use of ritonavir with cobicistat is not recommended, because of similar effects on CYP3A. Both ritonavir and cobicistat are potent inhibitors of CYP3A4. [51664] [58000] [58761] [58763]

Cobimetinib: (Major) Avoid the concurrent use of cobimetinib with ritonavir due to the risk of cobimetinib toxicity. Cobimetinib is a P-glycoprotein (P-gp) substrate as well as a CYP3A substrate in vitro; ritonavir is a P-gp inhibitor as well as a strong CYP3A inhibitor. In healthy subjects (n = 15), coadministration of a single 10 mg dose of cobimetinib with itraconazole (200 mg once daily for 14 days), another strong CYP3A4 inhibitor, increased the mean cobimetinib AUC by 6.7-fold (90% CI, 5.6 to 8) and the mean C_{max} by 3.2-fold (90% CI, 2.7 to 3.7). [28380] [34557] [47165] [60281]

Cocaine: (Moderate) Concurrent use of cocaine with ritonavir may result in elevated plasma concentrations of cocaine and ritonavir. Cocaine is a substrate/inhibitor of CYP3A4 and an inhibitor of CYP2D6; ritonavir is a substrate/inhibitor of both these enzymes. While single uses of topical cocaine for local anesthesia would not be expected to have clinically significant interactions, users of systemic cocaine could experience adverse events. [57067] [58664]

Codeine: (Moderate) Concomitant use of codeine with ritonavir may alter codeine plasma concentrations, resulting in an unpredictable effect such as reduced efficacy or symptoms of opioid withdrawal or prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage adjustment of codeine until stable drug effects are achieved. Discontinuation of ritonavir could alter codeine plasma concentrations, resulting in an unpredictable effect such as prolonged opioid adverse reactions or decreased opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to codeine. If ritonavir is discontinued, monitor the patient carefully and consider adjusting the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Ritonavir is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. CYP3A4 inhibitors may increase codeine-related adverse effects while CYP2D6 inhibitors may reduce efficacy. [33654] [34883] [47165]

Codeine; Guaifenesin: (Moderate) Concomitant use of codeine with ritonavir may alter codeine plasma concentrations, resulting in an unpredictable effect such as reduced efficacy or symptoms of opioid withdrawal or prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage adjustment of codeine until stable drug effects are achieved. Discontinuation of ritonavir could alter codeine plasma concentrations, resulting in an unpredictable effect such as prolonged opioid adverse reactions or decreased opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to codeine. If ritonavir is discontinued, monitor the patient carefully and consider adjusting the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Ritonavir is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. CYP3A4 inhibitors may increase codeine-related adverse effects while CYP2D6 inhibitors may reduce efficacy. [33654] [34883] [47165]

Codeine; Phenylephrine; Promethazine: (Major) Avoid coadministration of lopinavir with promethazine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Promethazine, a phenothiazine, is also associated with a possible risk for QT prolongation. [28225] [28341] [55578] [65157]

[\[65170\]](#) (Moderate) Concomitant use of codeine with ritonavir may alter codeine plasma concentrations, resulting in an unpredictable effect such as reduced efficacy or symptoms of opioid withdrawal or prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage adjustment of codeine until stable drug effects are achieved. Discontinuation of ritonavir could alter codeine plasma concentrations, resulting in an unpredictable effect such as prolonged opioid adverse reactions or decreased opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to codeine. If ritonavir is discontinued, monitor the patient carefully and consider adjusting the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Ritonavir is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. CYP3A4 inhibitors may increase codeine-related adverse effects while CYP2D6 inhibitors may reduce efficacy. [\[33654\]](#) [\[34883\]](#) [\[47165\]](#)

Codeine; Promethazine: (Major) Avoid coadministration of lopinavir with promethazine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Promethazine, a phenothiazine, is also associated with a possible risk for QT prolongation. [\[28225\]](#) [\[28341\]](#) [\[55578\]](#) [\[65157\]](#) [\[65170\]](#) (Moderate) Concomitant use of codeine with ritonavir may alter codeine plasma concentrations, resulting in an unpredictable effect such as reduced efficacy or symptoms of opioid withdrawal or prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage adjustment of codeine until stable drug effects are achieved. Discontinuation of ritonavir could alter codeine plasma concentrations, resulting in an unpredictable effect such as prolonged opioid adverse reactions or decreased opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to codeine. If ritonavir is discontinued, monitor the patient carefully and consider adjusting the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Ritonavir is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. CYP3A4 inhibitors may increase codeine-related adverse effects while CYP2D6 inhibitors may reduce efficacy. [\[33654\]](#) [\[34883\]](#) [\[47165\]](#)

Colchicine: (Major) Due to the risk for serious colchicine toxicity including multi-organ failure and death, avoid coadministration of colchicine and ritonavir in patients with normal renal and hepatic function unless the use of both agents is imperative. Coadministration is contraindicated in patients with renal or hepatic impairment because colchicine accumulation may be greater in these populations. Ritonavir can inhibit colchicine's metabolism via P-glycoprotein (P-gp) and CYP3A4, resulting in increased colchicine exposure. If coadministration in patients with normal renal and hepatic function cannot be avoided, adjust the dose of colchicine by either reducing the daily dose or the dosage frequency, and carefully monitor for colchicine toxicity. Specific dosage adjustment recommendations are available for the Colcris product for patients who have taken ritonavir in the past 14 days or require concurrent use: for prophylaxis of gout flares, if the original dose is 0.6 mg twice daily, decrease to 0.3 mg once daily or if the original dose is 0.6 mg once daily, decrease to 0.3 mg once every other day; for treatment of gout flares, give 0.6 mg as a single dose, then 0.3 mg 1 hour later, and do not repeat for at least 3 days; for familial Mediterranean fever, do not exceed a 0.6 mg/day. [\[27493\]](#) [\[28380\]](#) [\[34557\]](#) [\[34558\]](#) [\[36114\]](#) [\[61147\]](#)

Colchicine; Probenecid: (Major) Due to the risk for serious colchicine toxicity including multi-organ failure and death, avoid coadministration of colchicine and ritonavir in patients with normal renal and hepatic function unless the use of both agents is imperative. Coadministration is contraindicated in patients with renal or hepatic impairment because colchicine accumulation may be greater in these populations. Ritonavir can inhibit colchicine's metabolism via P-glycoprotein (P-gp) and CYP3A4, resulting in increased colchicine exposure. If coadministration in patients with normal renal and hepatic function cannot be avoided, adjust the dose of colchicine by either reducing the daily dose or the dosage frequency, and carefully monitor for colchicine toxicity. Specific dosage adjustment recommendations are available for the Colcris product for patients who have taken ritonavir in the past 14 days or require concurrent use: for prophylaxis of gout flares, if the original dose is 0.6 mg twice daily, decrease to 0.3 mg once daily or if the original dose is 0.6 mg once daily, decrease to 0.3 mg once every other day; for treatment of gout flares, give 0.6 mg as a single dose, then 0.3 mg 1 hour later, and do not repeat for at least 3 days; for familial Mediterranean fever, do not exceed a 0.6 mg/day. [\[27493\]](#) [\[28380\]](#) [\[34557\]](#) [\[34558\]](#) [\[36114\]](#) [\[61147\]](#)

Conivaptan: (Severe) Coadministration of conivaptan with strong CYP3A4 inhibitors like lopinavir; ritonavir is contraindicated. The plasma concentrations of both drugs may be elevated during concurrent use. Coadministration of conivaptan with ketoconazole, a potent CYP3A4 inhibitor, results in 4- and 11- fold increase in conivaptan Cmax and AUC, respectively; similar pharmacokinetic effects could be seen with the coadministration of conivaptan and lopinavir; ritonavir. In addition, conivaptan inhibits both CYP3A4 and P-glycoprotein; ritonavir is a substrate of both CYP3A4 and P-gp. Per the manufacturer of conivaptan, concomitant use of conivaptan with CYP3A4 substrates should be avoided. Subsequent treatment with CYP3A substrates may be initiated no sooner than 1 week after completion of conivaptan therapy. [\[28341\]](#) [\[31764\]](#) (Severe) Coadministration of conivaptan with strong CYP3A4 inhibitors like ritonavir is contraindicated. The plasma concentrations of both drugs may be elevated during concurrent use. Coadministration of conivaptan with ketoconazole, a potent CYP3A4 inhibitor, results in 4- and 11- fold increase in conivaptan Cmax and AUC, respectively; similar pharmacokinetic effects could be seen with the coadministration of conivaptan and ritonavir. In addition, conivaptan inhibits both CYP3A4 and P-glycoprotein (P-gp); ritonavir is a substrate of both CYP3A4 and P-gp. Per the manufacturer of conivaptan, concomitant use of conivaptan with CYP3A4 substrates should be avoided. Subsequent treatment with CYP3A substrates may be initiated no sooner than 1 week after completion of conivaptan therapy. [\[28315\]](#) [\[28341\]](#) [\[31764\]](#) [\[56579\]](#)

Conjugated Estrogens: (Moderate) In vitro and in vivo studies have shown that estrogens are metabolized partially by CYP3A4. Inhibitors of CYP3A4, such as ritonavir, may increase the exposure of conjugated estrogens resulting in an increased risk of estrogen-related side effects or endometrial hyperplasia. Therefore, when chronically coadministering ritonavir (more than 30 days) with conjugated estrogens, adequate diagnostic measures, including directed or random endometrial sampling when indicated by signs and symptoms of endometrial hyperplasia, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. Patients should report any breakthrough bleeding or adverse events to their prescribers. [\[28315\]](#) [\[56074\]](#)

Conjugated Estrogens; Bazedoxifene: (Moderate) In vitro and in vivo studies have shown that estrogens are metabolized partially by CYP3A4. Inhibitors of CYP3A4, such as ritonavir, may increase the exposure of conjugated estrogens resulting in an increased risk of estrogen-related side effects or endometrial hyperplasia. Therefore, when chronically coadministering ritonavir (more than 30 days) with

conjugated estrogens, adequate diagnostic measures, including directed or random endometrial sampling when indicated by signs and symptoms of endometrial hyperplasia, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. Patients should report any breakthrough bleeding or adverse events to their prescribers. [\[28315\]](#) [\[56074\]](#)

Conjugated Estrogens; Medroxyprogesterone: (Major) Coadministration of medroxyprogesterone, a CYP3A substrate with ritonavir, a strong CYP3A inhibitor should be avoided since it is expected to increase concentrations of medroxyprogesterone acetate. Formal drug interaction studies have not been conducted; however, medroxyprogesterone is metabolized primarily by hydroxylation via the CYP3A4 in vitro. [\[28380\]](#) [\[34557\]](#) [\[47165\]](#) [\[57648\]](#) (Moderate) In vitro and in vivo studies have shown that estrogens are metabolized partially by CYP3A4. Inhibitors of CYP3A4, such as ritonavir, may increase the exposure of conjugated estrogens resulting in an increased risk of estrogen-related side effects or endometrial hyperplasia. Therefore, when chronically coadministering ritonavir (more than 30 days) with conjugated estrogens, adequate diagnostic measures, including directed or random endometrial sampling when indicated by signs and symptoms of endometrial hyperplasia, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. Patients should report any breakthrough bleeding or adverse events to their prescribers. [\[28315\]](#) [\[56074\]](#)

Copanlisib: (Major) Avoid the concomitant use of copanlisib and ritonavir if possible; increased copanlisib exposure may occur. If coadministration cannot be avoided, reduce the copanlisib dose to 45 mg and monitor patients for copanlisib-related adverse events (e.g., hypertension, infection, and skin rash). Copanlisib is a CYP3A substrate; ritonavir is a strong CYP3A inhibitor. [\[47165\]](#) [\[62347\]](#)

Crizotinib: (Major) Avoid coadministration of lopinavir with crizotinib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Interrupt, dose reduce, or discontinue crizotinib therapy if QT prolongation occurs. Crizotinib can cause concentration-dependent QT prolongation. Lopinavir is associated with QT prolongation. [\[28341\]](#) [\[45458\]](#) [\[65157\]](#) [\[65170\]](#) (Major) Avoid coadministration of ritonavir with crizotinib due to increased plasma concentrations of crizotinib. If concomitant use is unavoidable, reduce the dose of crizotinib to 250 mg by mouth once daily; resume the original crizotinib dose after discontinuation of ritonavir. Crizotinib is a CYP3A substrate. ritonavir is a strong CYP3A4 inhibitor. Coadministration with one strong CYP3A inhibitor increased the AUC and C_{max} of single-dose crizotinib by 216% and 44%, respectively. Concomitant use with another strong CYP3A4 inhibitor increased the steady-state AUC and C_{max} of crizotinib by 57% and 33%, respectively, compared to crizotinib alone. [\[45458\]](#) [\[47165\]](#)

Cyclophosphamide: (Moderate) Use caution if cyclophosphamide is used concomitantly with ritonavir, and monitor for possible changes in the efficacy or toxicity profile of cyclophosphamide. The clinical significance of this interaction is unknown. Cyclophosphamide is a prodrug that is hydroxylated and activated primarily by CYP2B6; the contribution of CYP3A4 to the activation of cyclophosphamide is variable. Additional isoenzymes involved in the activation of cyclophosphamide include CYP2A6, 2C9, 2C18, and 2C19. N-dechloroethylation to therapeutically inactive but neurotoxic metabolites occurs primarily via CYP3A4. The active metabolites, 4-hydroxycyclophosphamide and aldophosphamide, are then inactivated by aldehyde dehydrogenase-mediated oxidation. Ritonavir is a strong CYP3A4 inhibitor as well as a moderate inhibitor of CYP2C9; conversion of cyclophosphamide to its active metabolites may be affected. The use of protease inhibitor-based regimens was found to be associated with a higher incidence of infections and neutropenia in patients receiving cyclophosphamide, doxorubicin, and etoposide (CDE) than use of a non-nucleoside reverse transcriptase inhibitor-based regimen. In vitro, coadministration with troleandomycin, a CYP3A4 inhibitor, had little-to-no effect on cyclophosphamide metabolism. However, concurrent use of cyclophosphamide conditioning therapy with itraconazole (a strong CYP3A4 inhibitor) and fluconazole (a moderate CYP3A4 inhibitor) in a randomized trial resulted in increases in serum bilirubin and creatinine, along with increased exposure to toxic cyclophosphamide metabolites (n = 197). [\[26577\]](#) [\[27058\]](#) [\[28045\]](#) [\[28057\]](#) [\[47165\]](#)

Cyclosporine: (Major) An interaction is anticipated to occur with all anti-retroviral protease inhibitors and cyclosporine, as all protease inhibitors inhibit CYP3A4. Cyclosporine toxicity, consisting of fatigue, headache, and GI distress, has been reported by a patient receiving cyclosporine and saquinavir. Prior to beginning saquinavir the patient had been receiving stable doses of cyclosporine resulting in trough concentrations of 150 to 200 mcg/ml. After receiving saquinavir for 3 days, the cyclosporine trough concentration increased to 580 mcg/ml. Dosages of both agents were decreased by 50% leading to resolution of symptoms. This interaction is probably due to CYP3A4 inhibition by saquinavir. Another possible mechanism is that both drugs have a high affinity for the drug efflux protein, P-glycoprotein, which may increase the absorption or decrease the clearance of the other drug. [\[2357\]](#) [\[28142\]](#) [\[28341\]](#) [\[28839\]](#) [\[28995\]](#) [\[32432\]](#) [\[4718\]](#) [\[5936\]](#)

Dabigatran: (Moderate) Increased serum concentrations of dabigatran are possible when dabigatran, a P-glycoprotein (P-gp) substrate, is coadministered with ritonavir, a P-gp inhibitor. Patients should be monitored for increased adverse effects of dabigatran. When dabigatran is administered for treatment or reduction in risk of recurrence of deep venous thrombosis (DVT) or pulmonary embolism (PE), or prophylaxis of DVT or PE following hip replacement surgery, avoid coadministration with P-gp inhibitors like ritonavir in patients with CrCl less than 50 mL/minute. When dabigatran is used in patients with non-valvular atrial fibrillation and severe renal impairment (CrCl less than 30 mL/minute), avoid coadministration with ritonavir, as serum concentrations of dabigatran are expected to be higher than when administered to patients with normal renal function. P-gp inhibition and renal impairment are the major independent factors that result in increased exposure to dabigatran. [\[27493\]](#) [\[28380\]](#) [\[42121\]](#)

Dabrafenib: (Major) The concomitant use of dabrafenib, a CYP3A4 substrate and a moderate CYP3A4 inducer, and lopinavir; ritonavir may result in altered levels of either agent; avoid concomitant use if possible. Ritonavir is a strong CYP3A4 inhibitor and a CYP3A4 substrate and inducer, while lopinavir is a CYP3A4 substrate. If another agent cannot be substituted and coadministration of these agents is unavoidable, monitor patients closely for dabrafenib or ritonavir adverse effects and/or reduced efficacy. [\[28341\]](#) [\[54802\]](#) (Major) The concomitant use of dabrafenib, a CYP3A4 substrate and a moderate CYP3A4 inducer, and ritonavir, a strong CYP3A4 inhibitor and a CYP3A4 substrate and inducer, may result in altered levels of either agent; avoid concomitant use if possible. If another agent cannot be substituted and coadministration of these agents is unavoidable, monitor patients closely for dabrafenib or ritonavir adverse effects and/or reduced efficacy. [\[28315\]](#) [\[54802\]](#)

Daclatasvir: (Major) The dose of daclatasvir, a CYP3A4 substrate, must be reduced to 30 mg PO once daily when administered in combination with strong CYP3A4 inhibitors, such as ritonavir. Taking these drugs together may increase daclatasvir serum

concentrations, and potentially increase the risk for adverse effects. In addition, the therapeutic effects of ritonavir, a P-glycoprotein (P-gp) substrate, may be increased by daclatasvir, a P-gp inhibitor. [28380] [34557] [47165] [60001]

Dapagliflozin: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [7238] [7335]

Dapagliflozin; Metformin: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [7238] [7335] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Dapagliflozin; Saxagliptin: (Major) The metabolism of saxagliptin is primarily mediated by CYP3A4/5. The saxagliptin dose is limited to 2.5 mg once daily when coadministered with a strong CYP 3A4/5 inhibitor such as the ritonavir component of lopinavir; ritonavir. In addition, new onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [28341] [30575] [36111] (Major) The metabolism of saxagliptin is primarily mediated by CYP3A4/5. The saxagliptin dose is limited to 2.5 mg once daily when coadministered with a strong CYP3A4/5 inhibitor such as ritonavir. New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have also been reported with use of anti-retroviral protease inhibitors, such as ritonavir. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [36111] [7238] [7335] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [7238] [7335]

Dapsone: (Moderate) Concurrent administration of dapsone with ritonavir may result in elevated dapsone plasma concentrations. Dapsone is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [11191] [47165] [58664]

Darifenacin: (Moderate) The daily dose of darifenacin should not exceed 7.5 mg PO when administered with ritonavir due to increased darifenacin exposure. Darifenacin is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. [30711] [47165]

Darolutamide: (Moderate) Monitor patients more frequently for darolutamide-related adverse reactions if coadministration with ritonavir is necessary due to the risk of increased darolutamide exposure; decrease the dose of darolutamide for grade 3 or 4 adverse reactions or for otherwise intolerable adverse reactions. Ritonavir is a P-glycoprotein (P-gp) inhibitor and a strong CYP3A4 inhibitor; darolutamide is a CYP3A4 substrate. Concomitant use with another combined P-gp inhibitor and strong CYP3A4 inhibitor increased the mean AUC and C_{max} of darolutamide by 1.7-fold and 1.4-fold, respectively. [28380] [34557] [47165] [64525]

Darunavir: (Major) Coadministration of darunavir with lopinavir is not recommended. Coadministration of darunavir with lopinavir; ritonavir resulted in decreased darunavir exposure by approximately 38% to 41% depending on lopinavir; ritonavir dose. Appropriate dose adjustments for this combination have not been established. [32432]

Darunavir; Cobicistat: (Severe) Use of ritonavir with cobicistat is not recommended, because of similar effects on CYP3A. Both ritonavir and cobicistat are potent inhibitors of CYP3A4. [51664] [58000] [58761] [58763] (Major) Coadministration of darunavir with lopinavir is not recommended. Coadministration of darunavir with lopinavir; ritonavir resulted in decreased darunavir exposure by approximately 38% to 41% depending on lopinavir; ritonavir dose. Appropriate dose adjustments for this combination have not been established. [32432]

Darunavir; Cobicistat; Emtricitabine; Tenofovir alafenamide: (Severe) Use of ritonavir with cobicistat is not recommended, because of similar effects on CYP3A. Both ritonavir and cobicistat are potent inhibitors of CYP3A4. [51664] [58000] [58761] [58763] (Major) Coadministration of darunavir with lopinavir is not recommended. Coadministration of darunavir with lopinavir; ritonavir resulted in decreased darunavir exposure by approximately 38% to 41% depending on lopinavir; ritonavir dose. Appropriate dose adjustments for this combination have not been established. [32432] (Moderate) Concurrent use of lopinavir with tenofovir alafenamide may result in elevated tenofovir serum concentrations. Tenofovir alafenamide is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. When 10 mg of tenofovir alafenamide was administered daily with lopinavir; ritonavir (800 mg/200 mg PO daily), the tenofovir C_{max} and AUC increased by 2.19-fold and 1.47-fold, respectively. Monitor for increased toxicities if these drugs are given together. [60269] [61510] [61511] [61513]

Dasabuvir; Ombitasvir; Paritaprevir; Ritonavir: (Major) Avoid coadministration of lopinavir with paritaprevir. Use of these drugs in combination has resulted in elevated paritaprevir serum concentrations. Paritaprevir is a substrate of the drugs transporter organic anion transporting polypeptide (OATP1B1); lopinavir is an OATP1B1 inhibitor. [58664] [61510] [61511] [61513]

Dasatinib: (Major) Avoid coadministration of dasatinib and ritonavir due to the potential for increased dasatinib exposure and subsequent toxicity including QT prolongation and torsade de pointes (TdP). An alternative to ritonavir with no or minimal enzyme inhibition potential is recommended if possible. If coadministration cannot be avoided, consider a dasatinib dose reduction to 40 mg PO daily if original dose was 140 mg daily, 20 mg PO daily if original dose was 100 mg daily, or 20 mg PO daily if original dose was 70 mg daily. Concomitant use of ritonavir is not recommended in patients receiving dasatinib 60 mg or 40 mg daily. If dasatinib is not tolerated after dose reduction, consider alternative therapies. If ritonavir is stopped, allow a washout of approximately 1 week before increasing the dasatinib dose. Dasatinib is a CYP3A4 substrate that has the potential to prolong the QT interval; ritonavir is a strong CYP3A4 inhibitor. Coadministration of another strong CYP3A4 inhibitor increased the mean C_{max} and AUC of dasatinib by 4-fold and 5-fold, respectively. [47165] [60087] (Major) Avoid coadministration of lopinavir with dasatinib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. In vitro studies have shown that dasatinib has the potential to prolong the QT interval. [28341] [32387] [60087] [65157] [65170]

Deferasirox: (Major) Deferasirox undergoes UGT metabolism, and ritonavir is a potent inducer of this enzyme system. The concomitant administration of deferasirox (single dose of 30 mg/kg) and the potent UGT inducer rifampin (i.e., rifampicin 600 mg/day for 9 days) resulted in a decrease in deferasirox AUC by 44%. Although specific drug interaction studies of deferasirox and ritonavir are not available, a similar interaction may occur. Avoid the concomitant use of ritonavir and deferasirox if possible. If ritonavir and deferasirox coadministration is necessary, consider increasing the initial dose of deferasirox. Monitor serum ferritin concentrations and clinical response for further modifications. [31807]

Deflazacort: (Major) Decrease deflazacort dose to one third of the recommended dosage when coadministered with ritonavir. Concurrent use may significantly increase concentrations of 21-desDFZ, the active metabolite of deflazacort, resulting in an increased risk of toxicity. Deflazacort is a CYP3A4 substrate; ritonavir is a strong inhibitor of CYP3A4. Administration of deflazacort with clarithromycin, a strong CYP3A4 inhibitor, increased total exposure to 21-desDFZ by about 3-fold. [47165] [61750]

Degarelix: (Major) Avoid coadministration of lopinavir with degarelix due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Androgen deprivation therapy (i.e., degarelix) may prolong the QT/QTc interval. [28341] [46869] [65157] [65170]

Delavirdine: (Moderate) Monitor for increased toxicity of ritonavir during coadministration of delavirdine. Appropriate doses of ritonavir in combination with delavirdine with respect to safety and efficacy have not been established. The exposure to ritonavir has been increased by 70% during concurrent administration of delavirdine. [28476] [46638] [47165]

Desipramine: (Moderate) A dose reduction of the tricyclic antidepressant (TCA) may be necessary when coadministered with ritonavir. Concurrent use may result in elevated TCA plasma concentrations. [47165]

Deutetrabenazine: (Major) Avoid coadministration of lopinavir with deutetrabenazine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. For patients taking a deutetrabenazine dosage more than 24 mg/day, assess the QTc interval before and after increasing the deutetrabenazine dosage or other medications that prolong the QTc interval. Both drugs are associated with QT prolongation. [28341] [61845] [65157] [65170]

Dexamethasone: (Major) Decreased plasma levels of lopinavir are seen when dexamethasone and lopinavir; ritonavir (Kaletra) coadministered. Use this treatment combination with caution and carefully monitor HIV treatment status, as decreased clinical efficacy of lopinavir; ritonavir may be seen. [28341] (Moderate) Close monitoring of therapeutic and adverse effects is required when dexamethasone is coadministered with ritonavir. Ritonavir inhibits CYP3A4 and dexamethasone is a CYP3A4 substrate. [4718] [5070] [5206]

Dexlansoprazole: (Moderate) Concurrent administration of dexlansoprazole with ritonavir may result in elevated dexlansoprazole plasma concentrations. Dexlansoprazole is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and monitoring for adverse effects are advised if these drugs are administered together. [40029] [47165] [58664]

Dexmedetomidine: (Moderate) Use caution if ritonavir is coadministered with dexmedetomidine due to the potential for decreased dexmedetomidine exposure which may decrease its efficacy. Limited data suggests that dexmedetomidine is metabolized by several enzymes, including CYP2C19. Ritonavir is an inducer of CYP2C19. [47165] [65210] [65222]

Dextroamphetamine: (Moderate) Warn patients that the risk of amphetamine toxicity may be increased during concurrent use of ritonavir, a strong CYP2D6 inhibitor. Amphetamines are partially metabolized by CYP2D6 and have serotonergic properties; inhibition of amphetamine metabolism may increase the risk of serotonin syndrome or other toxicity. If serotonin syndrome occurs, both the amphetamine and CYP2D6 inhibitor should be discontinued and appropriate medical treatment should be implemented. [25887] [29219] [33263] [47165] [57067]

Dextromethorphan; Diphenhydramine; Phenylephrine: (Moderate) Concurrent administration of diphenhydramine with ritonavir may result in elevated plasma concentrations of diphenhydramine. Diphenhydramine is a CYP2D6 substrate, and ritonavir is a CYP2D6 inhibitor. Caution and close monitoring are advised if these drugs are administered together. [34522] [34523] [47165] [58664]

Dextromethorphan; Promethazine: (Major) Avoid coadministration of lopinavir with promethazine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Promethazine, a phenothiazine, is also associated with a possible risk for QT prolongation. [28225] [28341] [55578] [65157] [65170]

Dextromethorphan; Quinidine: (Major) Avoid coadministration of lopinavir with quinidine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT

prolongation. Quinidine administration is associated with QT prolongation and torsade de pointes (TdP). [28341] [42280] [47357] [65157] [65170] (Major) Coadministration of HIV treatment doses of ritonavir and quinidine is contraindicated due to the potential for serious or life-threatening reactions, such as cardiac arrhythmias. Cautious consideration may be given to administering quinidine with boosting doses of ritonavir. Ritonavir is an inhibitor of CYP3A4 and increased plasma concentrations of drugs extensively metabolized by this enzyme, such as quinidine, should be expected with concurrent use. [28315] [42280] [46638] [47165] [47357]

Diazepam: (Major) CYP3A4 inhibitors, such as protease inhibitors, may reduce the metabolism of diazepam and increase the potential for benzodiazepine toxicity. Prolonged sedation and respiratory depression can occur. A decrease in the diazepam dose may be needed [28001] [28345] [28556] [47165] [55901]

Diclofenac: (Moderate) Concurrent administration of diclofenac with ritonavir may result in elevated diclofenac plasma concentrations. Diclofenac is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring for adverse effects are advised if these drugs are administered together. [11181] [47165] [58664]

Diclofenac; Misoprostol: (Moderate) Concurrent administration of diclofenac with ritonavir may result in elevated diclofenac plasma concentrations. Diclofenac is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring for adverse effects are advised if these drugs are administered together. [11181] [47165] [58664]

Dienogest; Estradiol valerate: (Moderate) Ritonavir has been shown to increase the metabolism of ethinyl estradiol. Ritonavir is a substrate and inhibitor of CYP3A4. It is not known if the effects of protease inhibitors are similar on estradiol; however, estradiol is metabolized by CYP3A4, similar to ethinyl estradiol. [28315]

Digoxin: (Major) In a pharmacokinetic study of 11 healthy men, increases in digoxin AUC (86%), volume of distribution, and half-life were seen, while renal and non-renal clearance decreased, when coadministered with ritonavir. It appears that this interaction is mediated by ritonavir's inhibition of P-glycoprotein-mediated renal tubular secretion of digoxin. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including digoxin) has not been evaluated. Measure serum digoxin concentrations before initiating ritonavir or lopinavir; ritonavir. Reduce digoxin concentrations by decreasing the digoxin dose by approximately 30 to 50% or by modifying the dosing frequency and continue monitoring. [28272] [28380] [30195]

Dihydrocodeine; Guaifenesin; Pseudoephedrine: (Moderate) Concomitant use of dihydrocodeine with ritonavir may increase dihydrocodeine plasma concentrations, resulting in greater metabolism by CYP2D6, increased dihydromorphine concentrations, and prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of dihydrocodeine until stable drug effects are achieved. Discontinuation of ritonavir could decrease dihydrocodeine plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to dihydrocodeine. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Ritonavir is a strong inhibitor of CYP3A4, an isoenzyme partially responsible for the metabolism of dihydrocodeine. [30282] [47165]

Dihydroergotamine: (Severe) Coadministration of ergot alkaloids with potent inhibitors of CYP3A4, like anti-retroviral protease inhibitors is considered contraindicated due to the risk of acute ergot toxicity (e.g., vasospasm leading to cerebral ischemia, peripheral ischemia and/or other serious effects). Several case reports have established the clinical significance of this interaction in the medical literature. In some cases, fatal interactions have occurred. [28142] [28341] [28731] [28839] [28995] [32432] [46638] [5018] [5044] [5623] [5747] [8102]

Diltiazem: (Major) Ritonavir is expected to decrease the hepatic CYP metabolism of diltiazem, resulting in increased diltiazem concentrations. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased diltiazem may be warranted. In addition, ritonavir and diltiazem both prolong the PR interval and caution for increased risk is recommended with coadministration. [4718] [5044]

Diphenhydramine: (Moderate) Concurrent administration of diphenhydramine with ritonavir may result in elevated plasma concentrations of diphenhydramine. Diphenhydramine is a CYP2D6 substrate, and ritonavir is a CYP2D6 inhibitor. Caution and close monitoring are advised if these drugs are administered together. [34522] [34523] [47165] [58664]

Diphenhydramine; Hydrocodone; Phenylephrine: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531] (Moderate) Concurrent administration of diphenhydramine with ritonavir may result in elevated plasma concentrations of diphenhydramine. Diphenhydramine is a CYP2D6 substrate, and ritonavir is a CYP2D6 inhibitor. Caution and close monitoring are advised if these drugs are administered together. [34522] [34523] [47165] [58664]

Diphenhydramine; Ibuprofen: (Moderate) Concurrent administration of diphenhydramine with ritonavir may result in elevated plasma concentrations of diphenhydramine. Diphenhydramine is a CYP2D6 substrate, and ritonavir is a CYP2D6 inhibitor. Caution and close monitoring are advised if these drugs are administered together. [34522] [34523] [47165] [58664]

Diphenhydramine; Naproxen: (Moderate) Concurrent administration of diphenhydramine with ritonavir may result in elevated plasma concentrations of diphenhydramine. Diphenhydramine is a CYP2D6 substrate, and ritonavir is a CYP2D6 inhibitor. Caution and close monitoring are advised if these drugs are administered together. [34522] [34523] [47165] [58664]

Diphenhydramine; Phenylephrine: (Moderate) Concurrent administration of diphenhydramine with ritonavir may result in elevated plasma concentrations of diphenhydramine. Diphenhydramine is a CYP2D6 substrate, and ritonavir is a CYP2D6 inhibitor. Caution and close monitoring are advised if these drugs are administered together. [\[34522\]](#) [\[34523\]](#) [\[47165\]](#) [\[58664\]](#)

Disopyramide: (Major) Avoid coadministration of lopinavir with disopyramide due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Disopyramide is associated with QT prolongation and torsade de pointes (TdP). [\[28228\]](#) [\[28341\]](#) [\[65157\]](#) [\[65170\]](#) (Major) Caution is warranted when ritonavir is coadministered with antiarrhythmics, including disopyramide. Ritonavir is an inhibitor of CYP3A4, and increased concentrations of disopyramide may be expected during coadministration. Therapeutic antiarrhythmic concentration monitoring is suggested when available. Monitor therapeutic response closely; dosage reduction may be needed. In some cases, the drug interaction may require more than 50% dosage reduction due to potent inhibitory effects and drug accumulation. Cardiac and neurologic events have been reported when ritonavir was concurrently administered with disopyramide. [\[28001\]](#) [\[28228\]](#) [\[28315\]](#)

Disulfiram: (Major) Oral solutions of ritonavir contain ethanol. Administration of ritonavir oral solution to patients receiving or who have recently received disulfiram may result in disulfiram-like reactions. A disulfiram reaction would not be expected to occur with non-ethanol containing formulations. [\[28315\]](#) [\[48545\]](#) (Major) The ingestion of ethanol by patients receiving disulfiram causes an extremely unpleasant reaction ('Antabuse Reaction') that can last from 30 minutes to several hours; however, the intensity and duration are dependent upon the disulfiram dosage. Oral solutions of lopinavir; ritonavir contain ethanol. Administration of lopinavir; ritonavir oral solution to patients receiving or who have recently received disulfiram may result in antabuse reactions. A disulfiram reaction would not be expected to occur with non-ethanol containing formulations. [\[28341\]](#) [\[48545\]](#)

Docetaxel: (Major) Avoid coadministration of docetaxel with lopinavir; ritonavir if possible due to increased plasma concentrations of docetaxel. If concomitant use is unavoidable, closely monitor for docetaxel-related adverse reactions and consider a 50% dose reduction of docetaxel. Docetaxel is a CYP3A4 substrate and lopinavir; ritonavir is a strong CYP3A4 inhibitor. Concomitant use with another strong CYP3A4 inhibitor increased docetaxel exposure by 2.2-fold. [\[28341\]](#) [\[56579\]](#) [\[60484\]](#) [\[63168\]](#) (Major) Avoid coadministration of docetaxel with ritonavir if possible due to increased plasma concentrations of docetaxel. If concomitant use is unavoidable, closely monitor for docetaxel-related adverse reactions and consider a 50% dose reduction of docetaxel. Docetaxel is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Concomitant use with another strong CYP3A4 inhibitor increased docetaxel exposure by 2.2-fold. [\[47165\]](#) [\[60484\]](#)

Dofetilide: (Major) Avoid coadministration of lopinavir with dofetilide due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Dofetilide, a Class III antiarrhythmic agent, is associated with a well-established risk of QT prolongation and torsade de pointes (TdP). [\[28221\]](#) [\[28341\]](#) [\[28432\]](#) [\[28457\]](#) [\[65157\]](#) [\[65170\]](#) (Moderate) Concomitant use of dofetilide and ritonavir may increase the risk of QT prolongation and torsade de pointes (TdP) due to increased dofetilide exposure. Dofetilide is metabolized to a small degree by CYP3A4; ritonavir is a potent inhibitor of CYP3A4. [\[28221\]](#) [\[47165\]](#)

Dolasetron: (Major) Avoid coadministration of lopinavir with dolasetron due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Dolasetron has been associated with a dose-dependent prolongation in the QT, PR, and QRS intervals on an electrocardiogram. [\[28341\]](#) [\[42844\]](#) [\[65157\]](#) [\[65170\]](#)

Dolutegravir; Rilpivirine: (Major) Avoid coadministration of lopinavir with rilpivirine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Supratherapeutic doses of rilpivirine (75 to 300 mg/day) have caused QT prolongation. [\[28341\]](#) [\[44376\]](#) [\[65157\]](#) [\[65170\]](#)

Donepezil: (Major) Avoid coadministration of lopinavir with donepezil due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Case reports indicate that QT prolongation and torsade de pointes (TdP) can occur during donepezil therapy. [\[28341\]](#) [\[59321\]](#) [\[59322\]](#) [\[65157\]](#) [\[65170\]](#) (Moderate) The plasma concentrations of donepezil may be elevated when administered concurrently with ritonavir. Clinical monitoring for adverse effects, such as GI or cholinergic effects, is recommended during coadministration. Ritonavir is a strong inhibitor of CYP3A4 and a CYP2D6 inhibitor, while donepezil is a CYP3A4 and CYP2D6 substrate. [\[29640\]](#) [\[47165\]](#)

Donepezil; Memantine: (Major) Avoid coadministration of lopinavir with donepezil due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Case reports indicate that QT prolongation and torsade de pointes (TdP) can occur during donepezil therapy. [\[28341\]](#) [\[59321\]](#) [\[59322\]](#) [\[65157\]](#) [\[65170\]](#) (Moderate) The plasma concentrations of donepezil may be elevated when administered concurrently with ritonavir. Clinical monitoring for adverse effects, such as GI or cholinergic effects, is recommended during coadministration. Ritonavir is a strong inhibitor of CYP3A4 and a CYP2D6 inhibitor, while donepezil is a CYP3A4 and CYP2D6 substrate. [\[29640\]](#) [\[47165\]](#)

Doravirine: (Minor) Coadministration of doravirine and ritonavir may result in increased doravirine plasma concentrations. Doravirine is a CYP3A4 substrate; ritonavir is a strong inhibitor. In a drug interaction study, concurrent use of ritonavir increased doravirine exposure by more than 3-fold; however, this increase was not considered clinically significant. [\[63484\]](#)

Doravirine; Lamivudine; Tenofovir disoproxil fumarate: (Moderate) Caution is advised when administering tenofovir, PMPA, a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate, concurrently with inhibitors of P-gp and BCRP, such as ritonavir. Coadministration may result in increased absorption of tenofovir. Monitor for tenofovir-associated adverse reactions. [\[28193\]](#) [\[58664\]](#) (Minor) Coadministration of doravirine and ritonavir may result in increased doravirine plasma concentrations. Doravirine is a CYP3A4 substrate; ritonavir is a strong inhibitor. In a drug interaction study, concurrent use of ritonavir increased doravirine exposure by more than 3-fold; however, this increase was not considered clinically significant. [\[63484\]](#) (Minor) There are varying results in reports of

an interaction between tenofovir and lopinavir; ritonavir. In one report, the concurrent administration of tenofovir with lopinavir; ritonavir increased tenofovir C_{max} 31%, AUC 34%, and C_{min} 29%, with slight (15%) decreases in lopinavir C_{max} and AUC; the alterations may be a food effect rather than a drug-drug interaction. In another report, lopinavir; ritonavir (400 mg; 100 mg PO twice daily for 14 days) increased the tenofovir (300 mg/day PO) C_{min} 51% and AUC 32%, with no effect seen on lopinavir; ritonavir pharmacokinetics. While the clinical significance of this interaction is unknown, and is suspected to be insignificant, patients receiving lopinavir; ritonavir with tenofovir should be monitored for tenofovir-associated adverse events. [46638]

Dorzolamide; Timolol: (Moderate) Timolol is significantly metabolized by CYP2D6 isoenzymes. CYP2D6 inhibitors, such as ritonavir, may impair timolol metabolism; the clinical significance of such interactions is unknown. [5044] [5270]

Doxazosin: (Moderate) Monitor blood pressure and for signs of hypotension during coadministration. The plasma concentrations of doxazosin may be elevated when administered concurrently with ritonavir. Ritonavir is a strong CYP3A4 inhibitor; doxazosin is a CYP3A4 substrate. Coadministration of doxazosin with a moderate CYP3A4 inhibitor resulted in a 10% increase in mean AUC and an insignificant increase in mean C_{max} and mean half-life of doxazosin. Although not studied in combination with doxazosin, strong CYP3A4 inhibitors may have a larger impact on doxazosin concentrations and therefore should be used with caution. [29824] [47165] [56579]

Doxepin: (Moderate) A dose reduction of the tricyclic antidepressant (TCA) may be necessary when coadministered with ritonavir. Concurrent use may result in elevated TCA plasma concentrations. [47165]

Doxercalciferol: (Moderate) Protease inhibitors may decrease efficacy of doxercalciferol. Doxercalciferol is converted in the liver to 1,25-dihydroxyergocalciferol, the major active metabolite, and 1- α , 24-dihydroxyvitamin D₂, a minor metabolite. Although not specifically studied, cytochrome P450 enzyme inhibitors, including protease inhibitors, may inhibit the 25-hydroxylation of doxercalciferol, thereby decreasing the formation of the active metabolite and thus, decreasing efficacy. Patients should be monitored for a decrease in efficacy if these drugs are administered together. [30802] [49493]

Doxorubicin Liposomal: (Major) Avoid coadministration of ritonavir with doxorubicin due to increased systemic exposure of doxorubicin resulting in increased treatment-related adverse reactions. Ritonavir is a strong CYP3A4 inhibitor and a P-gp inhibitor; doxorubicin is a CYP3A4 and P-gp substrate. Concurrent use of CYP3A4 and/or P-gp inhibitors with doxorubicin has resulted in clinically significant interactions. [47165] [56361]

Doxorubicin: (Major) Avoid coadministration of ritonavir with doxorubicin due to increased systemic exposure of doxorubicin resulting in increased treatment-related adverse reactions. Ritonavir is a strong CYP3A4 inhibitor and a P-gp inhibitor; doxorubicin is a CYP3A4 and P-gp substrate. Concurrent use of CYP3A4 and/or P-gp inhibitors with doxorubicin has resulted in clinically significant interactions. [47165] [56361]

Dronabinol: (Major) Use caution if coadministration of dronabinol with ritonavir is necessary, and closely monitor for an increase in dronabinol-related adverse reactions (e.g., cognitive impairment, psychosis, seizures, and hemodynamic instability, as well as feeling high, dizziness, confusion, somnolence). Ritonavir is a strong inhibitor of CYP3A4 and a moderate CYP2C9 inducer; it is contraindicated with sensitive drugs that are highly dependent on CYP3A4/5 for clearance. Dronabinol is a CYP2C9 and 3A4 substrate; concomitant use may result in elevated plasma concentrations of dronabinol. [30431] [47165] [60951]

Dronedarone: (Severe) Coadministration of lopinavir; ritonavir with dronedarone is contraindicated due to the potential for additive QT prolongation. Dronedarone is highly dependent on CYP3A for clearance. Dronedarone administration is associated with a dose-related increase in the QTc interval. The increase in QTc is approximately 10 milliseconds at doses of 400 mg twice daily (the FDA-approved dose) and up to 25 milliseconds at doses of 1,600 mg twice daily. Lopinavir; ritonavir is a potent CYP3A inhibitor and is also associated with QT prolongation. [28341] [36101] (Severe) The concomitant use of dronedarone and ritonavir is contraindicated. Dronedarone is metabolized by CYP3A, is a moderate inhibitor of CYP3A, and is an inhibitor of P-gp. Ritonavir is a strong inhibitor of CYP3A4, is an inducer of CYP3A, and is a substrate of CYP3A and P-gp. Repeated doses of ketoconazole, also a strong CYP3A4 inhibitor, increased dronedarone exposure 17-fold and increased dronedarone C_{max} 9-fold. Furthermore, coadministration of dronedarone and ritonavir may, theoretically, result in decreased concentrations of dronedarone due to CYP3A induction by ritonavir; the net effect on dronedarone plasma concentrations is not known. However, no data exist regarding the safe administration of dronedarone with strong CYP3A4 inhibitors; therefore, concomitant use is contraindicated. Also, the effects of dronedarone on the pharmacokinetics of ritonavir have not been described, although an increase in ritonavir serum concentrations is possible. [36101]

Droperidol: (Major) Avoid coadministration of lopinavir with droperidol due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Initiate droperidol at a low dose and titrate as needed to achieve the desired effect. Lopinavir is associated with QT prolongation. Droperidol is associated with an established risk for QT prolongation and torsade de pointes (TdP). [28235] [28236] [28237] [28341] [28737] [51289] [65157] [65170]

Drospirenone; Estradiol: (Moderate) Ritonavir has been shown to increase the metabolism of ethinyl estradiol. Ritonavir is a substrate and inhibitor of CYP3A4. It is not known if the effects of protease inhibitors are similar on estradiol; however, estradiol is metabolized by CYP3A4, similar to ethinyl estradiol. [28315]

Drospirenone; Ethinyl Estradiol: (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and C_{max} by 32%. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [46638] [5044]

Drospirenone; Ethinyl Estradiol; Levomefolate: (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and C_{max} by 32%. Women receiving hormonal

contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [\[46638\]](#) [\[5044\]](#)

Dutasteride: (Moderate) Concurrent administration of dutasteride with protease inhibitors may result in elevated dutasteride plasma concentrations. Dutasteride is metabolized by the hepatic isoenzyme CYP3A4; protease inhibitors are potent inhibitors of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[28001\]](#) [\[28875\]](#)

Dutasteride; Tamsulosin: (Major) Plasma concentrations of tamsulosin may be increased with concomitant use of anti-retroviral protease inhibitors. Tamsulosin is extensively metabolized by CYP3A4 and CYP2D6 hepatic enzymes. In clinical evaluation, concomitant treatment with a strong CYP3A4 inhibitor resulted in significant increases in tamsulosin exposure. Such increases in tamsulosin concentrations may be expected to produce clinically significant and potentially serious side effects, such as hypotension. Therefore, concomitant use of tamsulosin with a strong CYP3A4 inhibitor, or an agent with both CYP3A4 and CYP2D6 inhibitor activity, should be avoided. [\[29677\]](#) [\[4194\]](#) [\[8102\]](#) (Moderate) Concurrent administration of dutasteride with protease inhibitors may result in elevated dutasteride plasma concentrations. Dutasteride is metabolized by the hepatic isoenzyme CYP3A4; protease inhibitors are potent inhibitors of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[28001\]](#) [\[28875\]](#)

Duvelisib: (Major) Reduce duvelisib dose to 15 mg PO twice daily and monitor for increased toxicity when coadministered with ritonavir. Coadministration may increase the exposure of duvelisib. Duvelisib is a CYP3A substrate; ritonavir is a strong CYP3A inhibitor. The increase in exposure to duvelisib is estimated to be approximately 2-fold when used concomitantly with strong CYP3A inhibitors such as ritonavir. [\[47165\]](#) [\[63571\]](#)

Echinacea: (Moderate) Use Echinacea sp. with caution in patients taking medications for human immunodeficiency virus (HIV) infection. Some experts have suggested that Echinacea's effects on the immune system might cause problems for patients with HIV infection, particularly with long-term use. There may be less risk with short-term use (less than 2 weeks). A few pharmacokinetic studies have shown reductions in blood levels of some antiretroviral medications when Echinacea was given, presumably due to CYP induction. However, more study is needed for various HIV treatment regimens. Of the agents studied, the interactions do not appear to be significant or to require dose adjustments at the time of use. Although no dose adjustments are required, monitoring drug concentrations may give reassurance during co-administration. Monitor viral load and other parameters carefully during therapy. [\[25398\]](#) [\[30456\]](#) [\[61924\]](#) [\[61926\]](#) [\[61927\]](#)

Edoxaban: (Moderate) Coadministration of edoxaban and ritonavir may result in increased concentrations of edoxaban. Edoxaban is a P-glycoprotein (P-gp) substrate and ritonavir is a P-gp inhibitor. Increased concentrations of edoxaban may occur during concomitant use of ritonavir; monitor for increased adverse effects of edoxaban. Dosage reduction may be considered for patients being treated for deep venous thrombosis (DVT) or pulmonary embolism. [\[28315\]](#) [\[58685\]](#)

Efavirenz: (Major) Avoid coadministration of lopinavir; ritonavir with efavirenz due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Additionally, increase the dose of lopinavir; ritonavir to 500/125 mg and administer twice daily in adults; do not use once daily administration. Induction of CYP3A4 by efavirenz may decrease lopinavir concentrations. Both drugs have been associated with QT prolongation. [\[28341\]](#) [\[28442\]](#) [\[32514\]](#) [\[42452\]](#) [\[46638\]](#) [\[51080\]](#) (Moderate) Monitor for elevation of liver enzymes and for adverse clinical experiences (e.g., dizziness, nausea, paresthesia) when efavirenz is coadministered with ritonavir. Concurrent use is expected to result in increased concentrations of both drugs. [\[28442\]](#) [\[47165\]](#)

Efavirenz; Emtricitabine; Tenofovir: (Major) Avoid coadministration of lopinavir; ritonavir with efavirenz due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Additionally, increase the dose of lopinavir; ritonavir to 500/125 mg and administer twice daily in adults; do not use once daily administration. Induction of CYP3A4 by efavirenz may decrease lopinavir concentrations. Both drugs have been associated with QT prolongation. [\[28341\]](#) [\[28442\]](#) [\[32514\]](#) [\[42452\]](#) [\[46638\]](#) [\[51080\]](#) (Moderate) Caution is advised when administering tenofovir, PMPA, a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate, concurrently with inhibitors of P-gp and BCRP, such as ritonavir. Coadministration may result in increased absorption of tenofovir. Monitor for tenofovir-associated adverse reactions. [\[28193\]](#) [\[58664\]](#) (Moderate) Monitor for elevation of liver enzymes and for adverse clinical experiences (e.g., dizziness, nausea, paresthesia) when efavirenz is coadministered with ritonavir. Concurrent use is expected to result in increased concentrations of both drugs. [\[28442\]](#) [\[47165\]](#) (Minor) There are varying results in reports of an interaction between tenofovir and lopinavir; ritonavir. In one report, the concurrent administration of tenofovir with lopinavir; ritonavir increased tenofovir C_{max} 31%, AUC 34%, and C_{min} 29%, with slight (15%) decreases in lopinavir C_{max} and AUC; the alterations may be a food effect rather than a drug-drug interaction. In another report, lopinavir; ritonavir (400 mg; 100 mg PO twice daily for 14 days) increased the tenofovir (300 mg/day PO) C_{min} 51% and AUC 32%, with no effect seen on lopinavir; ritonavir pharmacokinetics. While the clinical significance of this interaction is unknown, and is suspected to be insignificant, patients receiving lopinavir; ritonavir with tenofovir should be monitored for tenofovir-associated adverse events. [\[46638\]](#)

Efavirenz; Lamivudine; Tenofovir Disoproxil Fumarate: (Major) Avoid coadministration of lopinavir; ritonavir with efavirenz due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Additionally, increase the dose of lopinavir; ritonavir to 500/125 mg and administer twice daily in adults; do not use once daily administration. Induction of CYP3A4 by efavirenz may decrease lopinavir concentrations. Both drugs have been associated with QT prolongation. [\[28341\]](#) [\[28442\]](#) [\[32514\]](#) [\[42452\]](#) [\[46638\]](#) [\[51080\]](#) (Moderate) Caution is advised when administering tenofovir, PMPA, a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate, concurrently with inhibitors of P-gp and BCRP, such as ritonavir. Coadministration may result in increased absorption of tenofovir. Monitor for tenofovir-associated adverse reactions. [\[28193\]](#) [\[58664\]](#) (Moderate) Monitor for elevation of liver enzymes and for adverse clinical experiences (e.g., dizziness, nausea, paresthesia) when efavirenz is coadministered with ritonavir. Concurrent use is expected to result in increased concentrations of both drugs. [\[28442\]](#)

[47165] (Minor) There are varying results in reports of an interaction between tenofovir and lopinavir; ritonavir. In one report, the concurrent administration of tenofovir with lopinavir; ritonavir increased tenofovir C_{max} 31%, AUC 34%, and C_{min} 29%, with slight (15%) decreases in lopinavir C_{max} and AUC; the alterations may be a food effect rather than a drug-drug interaction. In another report, lopinavir; ritonavir (400 mg; 100 mg PO twice daily for 14 days) increased the tenofovir (300 mg/day PO) C_{min} 51% and AUC 32%, with no effect seen on lopinavir; ritonavir pharmacokinetics. While the clinical significance of this interaction is unknown, and is suspected to be insignificant, patients receiving lopinavir; ritonavir with tenofovir should be monitored for tenofovir-associated adverse events. **[46638]**

Elagolix: (Major) Concomitant use of elagolix 200 mg twice daily and lopinavir for more than 1 month is not recommended. Limit concomitant use of elagolix 150 mg once daily and lopinavir to 6 months. Monitor for elagolix-related side effects and reduced response to lopinavir. Elagolix is a CYP3A substrate and a weak to moderate CYP3A4 inducer; lopinavir is a strong inhibitor of CYP3A and a CYP3A4 substrate. Coadministration may increase elagolix plasma concentrations and decrease lopinavir concentrations. In drug interaction studies, coadministration of elagolix with another strong CYP3A inhibitor increased the C_{max} and AUC of elagolix by 77% and 120%, respectively. **[28341]** **[63387]** (Major) Concomitant use of elagolix 200 mg twice daily and ritonavir for more than 1 month is not recommended. Limit concomitant use of elagolix 150 mg once daily and ritonavir to 6 months. Monitor for elagolix-related side effects and reduced response to ritonavir. Elagolix is a CYP3A substrate and a weak to moderate CYP3A4 inducer; ritonavir is a strong inhibitor of CYP3A and a CYP3A4 substrate. Coadministration may increase elagolix plasma concentrations and decrease ritonavir concentrations. In drug interaction studies, coadministration of elagolix with another strong CYP3A inhibitor increased the C_{max} and AUC of elagolix by 77% and 120%, respectively. **[28341]** **[63387]**

Elbasvir; Grazoprevir: (Severe) Concurrent administration of elbasvir; grazoprevir with lopinavir; ritonavir is contraindicated. Use of these drugs together is expected to significantly increase the plasma concentrations of elbasvir and grazoprevir, and may result in adverse effects (i.e., elevated ALT concentrations). Lopinavir; ritonavir is an inhibitor of the hepatic enzyme CYP3A and the organic anion transporting protein (OATP1B1). Elbasvir and grazoprevir are metabolized by CYP3A, and grazoprevir is also a substrate of OATP1B1/3. **[28341]** **[60523]** **[61510]** **[61511]** **[61513]** (Major) Concurrent administration of elbasvir with ritonavir should be avoided if possible. Use of these drugs together is expected to significantly increase the plasma concentrations of elbasvir, and may result in adverse effects (i.e., elevated ALT concentrations and hepatotoxicity). Ritonavir is a strong inhibitor of the hepatic enzyme CYP3A, while elbasvir is metabolized by CYP3A. **[47165]** **[60523]** (Major) Concurrent administration of grazoprevir with ritonavir should be avoided if possible. Use of these drugs together is expected to significantly increase the plasma concentrations of grazoprevir, and may result in adverse effects (i.e., elevated ALT concentrations and hepatotoxicity). Ritonavir is a strong inhibitor of the hepatic enzyme CYP3A, while grazoprevir is metabolized by CYP3A. In addition, concentrations of ritonavir (also a CYP3A substrate) may be increased when given with grazoprevir (a weak CYP3A inhibitor). **[47165]** **[60523]**

Eletriptan: (Severe) Eletriptan is contraindicated for use within 72 hours of using any drug that is a potent CYP3A4 inhibitor as described in the prescribing information of the interacting drug including protease inhibitors. Eletriptan is metabolized via CYP3A4, and coadministration with protease inhibitors may cause increased eletriptan concentrations and thus toxicity. **[28341]** **[47165]**

Elexacaftor; tezacaftor; ivacaftor: (Major) If ritonavir and ivacaftor are taken together, administer ivacaftor at the usual recommended dose but reduce the frequency to twice weekly. Ivacaftor is a CYP3A substrate and ritonavir is a CYP3A inhibitor. Coadministration with another strong CYP3A inhibitor increased ivacaftor exposure by 8.5-fold. **[48524]** (Major) Reduce the dosing frequency of elexacaftor; tezacaftor; ivacaftor when coadministered with ritonavir; coadministration may increase elexacaftor; tezacaftor; ivacaftor exposure and adverse reactions. When combined, dose 2 elexacaftor/tezacaftor/ivacaftor combination tablets twice a week, approximately 3 to 4 days apart (i.e., Day 1 and Day 4). The evening dose of ivacaftor should not be taken. Elexacaftor, tezacaftor, and ivacaftor are CYP3A4 substrates (ivacaftor is a sensitive substrate); ritonavir is a strong CYP3A4 inhibitor. Coadministration of a strong CYP3A4 inhibitor increased elexacaftor exposure by 2.8-fold, tezacaftor exposure by 4.5-fold, and ivacaftor exposure by 15.6-fold. **[47165]** **[64697]** (Major) Reduce the dosing frequency of tezacaftor; ivacaftor when coadministered with ritonavir; coadministration may increase tezacaftor; ivacaftor exposure and adverse reactions. When combined, dose 1 tezacaftor; ivacaftor combination tablet twice a week, approximately 3 to 4 days apart (i.e., Day 1 and Day 4). The evening dose of ivacaftor should not be taken. Both tezacaftor and ivacaftor are CYP3A substrates (ivacaftor is a sensitive substrate); ritonavir is a strong CYP3A inhibitor. Coadministration of a strong CYP3A inhibitor increased tezacaftor and ivacaftor exposure 4- and 15.6-fold, respectively. **[47165]** **[62870]**

Eliglustat: (Major) Avoid coadministration of lopinavir with eliglustat due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Eliglustat is predicted to cause PR, QRS, and/or QT prolongation at significantly elevated plasma concentrations. **[28341]** **[57803]** **[65157]** **[65170]** (Major) Coadministration of eliglustat and ritonavir is contraindicated in intermediate or poor CYP2D6 metabolizers (IMs or PMs). In extensive CYP2D6 metabolizers (EMs), coadministration of these agents requires dosage reduction of eliglustat to 84 mg PO once daily. The coadministration of eliglustat with ritonavir and a moderate or strong CYP2D6 inhibitor is contraindicated in all patients. Eliglustat is a CYP3A and CYP2D6 substrate. Coadministration of eliglustat with CYP3A inhibitors, such as ritonavir, increases eliglustat exposure and the risk of serious adverse events (e.g., QT prolongation and cardiac arrhythmias); this risk is the highest in CYP2D6 IMs and PMs because a larger portion of the eliglustat dose is metabolized via CYP3A. **[28341]** **[47165]** **[57803]**

Eltrombopag: (Moderate) Eltrombopag is metabolized by CYP1A2. The significance of administering inducers of CYP1A2, such as ritonavir, on the systemic exposure of eltrombopag has not been established. Monitor patients for a decrease in the efficacy of eltrombopag if these drugs are coadministered. **[27493]** **[28315]** **[40392]**

Eluxadoline: (Major) When administered concurrently with lopinavir, the dose of eluxadoline must be reduced to 75 mg PO twice daily, and the patient should be closely monitored for eluxadoline-related adverse effects (i.e., decreased mental and physical acuity). Eluxadoline is a substrate of the organic anion-transporting peptide (OATP1B1); lopinavir is an OATP1B1 inhibitor. Advise patients against driving or operating machinery until the combine effects of these drugs on the individual patient is known. **[59741]** **[61510]** **[61511]** **[61513]** (Major) When administered concurrently with ritonavir, the dose of eluxadoline must be reduced to 75 mg PO twice daily, and the patient should be closely monitored for eluxadoline-related adverse effects (i.e., decreased mental and physical acuity). Advise patients against driving or operating machinery until the combine effects of these drugs on the individual patient is known. Eluxadoline is a substrate of the organic anion-transporting peptide (OATP1B1); ritonavir is an OATP1B1 inhibitor. **[59741]**

Elvitegravir: (Moderate) Concurrent administration of elvitegravir with ritonavir may result in elevated elvitegravir plasma concentrations. Elvitegravir is a substrate of the hepatic isoenzyme CYP3A4. Ritonavir inhibits the CYP3A4 enzyme. Caution and close monitoring are advised if these drugs are administered together. [51664] [58001] [58664]

Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Alafenamide: (Severe) Use of ritonavir with cobicistat is not recommended, because of similar effects on CYP3A. Both ritonavir and cobicistat are potent inhibitors of CYP3A4. [51664] [58000] [58761] [58763] (Moderate) Concurrent administration of elvitegravir with ritonavir may result in elevated elvitegravir plasma concentrations. Elvitegravir is a substrate of the hepatic isoenzyme CYP3A4. Ritonavir inhibits the CYP3A4 enzyme. Caution and close monitoring are advised if these drugs are administered together. [51664] [58001] [58664] (Moderate) Concurrent use of lopinavir with tenofovir alafenamide may result in elevated tenofovir serum concentrations. Tenofovir alafenamide is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. When 10 mg of tenofovir alafenamide was administered daily with lopinavir; ritonavir (800 mg/200 mg PO daily), the tenofovir C_{max} and AUC increased by 2.19-fold and 1.47-fold, respectively. Monitor for increased toxicities if these drugs are given together. [60269] [61510] [61511] [61513]

Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Disoproxil Fumarate: (Severe) Use of ritonavir with cobicistat is not recommended, because of similar effects on CYP3A. Both ritonavir and cobicistat are potent inhibitors of CYP3A4. [51664] [58000] [58761] [58763] (Moderate) Caution is advised when administering tenofovir, PMPA, a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate, concurrently with inhibitors of P-gp and BCRP, such as ritonavir. Coadministration may result in increased absorption of tenofovir. Monitor for tenofovir-associated adverse reactions. [28193] [58664] (Moderate) Concurrent administration of elvitegravir with ritonavir may result in elevated elvitegravir plasma concentrations. Elvitegravir is a substrate of the hepatic isoenzyme CYP3A4. Ritonavir inhibits the CYP3A4 enzyme. Caution and close monitoring are advised if these drugs are administered together. [51664] [58001] [58664] (Minor) There are varying results in reports of an interaction between tenofovir and lopinavir; ritonavir. In one report, the concurrent administration of tenofovir with lopinavir; ritonavir increased tenofovir C_{max} 31%, AUC 34%, and C_{min} 29%, with slight (15%) decreases in lopinavir C_{max} and AUC; the alterations may be a food effect rather than a drug-drug interaction. In another report, lopinavir; ritonavir (400 mg; 100 mg PO twice daily for 14 days) increased the tenofovir (300 mg/day PO) C_{min} 51% and AUC 32%, with no effect seen on lopinavir; ritonavir pharmacokinetics. While the clinical significance of this interaction is unknown, and is suspected to be insignificant, patients receiving lopinavir; ritonavir with tenofovir should be monitored for tenofovir-associated adverse events. [46638]

Empagliflozin: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [7238] [7335]

Empagliflozin; Linagliptin: (Moderate) Monitor for changes in glycemic control, specifically hyperglycemia, if ritonavir is administered concurrently with linagliptin. New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. [28315] [30575] [31240] [34557] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [7238] [7335] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy, such as linagliptin, should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [28341] [30575]

Empagliflozin; Linagliptin; Metformin: (Moderate) Monitor for changes in glycemic control, specifically hyperglycemia, if ritonavir is administered concurrently with linagliptin. New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. [28315] [30575] [31240] [34557] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [7238] [7335] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy, such as linagliptin, should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [28341] [30575] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Empagliflozin; Metformin: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [7238] [7335] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Emtricitabine; Rilpivirine; Tenofovir alafenamide: (Major) Avoid coadministration of lopinavir with rilpivirine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Supratherapeutic doses of rilpivirine (75 to 300 mg/day) have caused QT prolongation. [28341] [44376] [65157] [65170] (Moderate) Concurrent use of lopinavir with tenofovir alafenamide may result in elevated tenofovir serum concentrations. Tenofovir alafenamide is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. When 10 mg of tenofovir alafenamide was administered daily with lopinavir; ritonavir (800 mg/200 mg PO daily), the tenofovir C_{max} and AUC increased by 2.19-fold and 1.47-fold, respectively. Monitor for increased toxicities if these drugs are given together. [60269] [61510] [61511] [61513]

Emtricitabine; Rilpivirine; Tenofovir disoproxil fumarate: (Major) Avoid coadministration of lopinavir with rilpivirine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Supratherapeutic doses of rilpivirine (75 to 300 mg/day) have caused QT prolongation. [28341] [44376] [65157] [65170] (Moderate) Caution is advised when administering tenofovir, PMPA, a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate, concurrently with inhibitors of P-gp and BCRP, such as ritonavir. Coadministration may result in increased absorption of tenofovir. Monitor for tenofovir-associated adverse reactions. [28193] [58664] (Minor) There are varying results in reports of an interaction between tenofovir and lopinavir; ritonavir. In one report, the concurrent administration of tenofovir with lopinavir; ritonavir increased tenofovir C_{max} 31%, AUC 34%, and C_{min} 29%, with slight (15%) decreases in lopinavir C_{max} and AUC; the alterations may be a food effect rather than a drug-drug interaction. In another report, lopinavir; ritonavir (400 mg; 100 mg PO twice daily for 14 days) increased the tenofovir (300 mg/day PO) C_{min} 51% and AUC 32%, with no effect seen on lopinavir; ritonavir pharmacokinetics. While the clinical significance of this interaction is unknown, and is suspected to be insignificant, patients receiving lopinavir; ritonavir with tenofovir should be monitored for tenofovir-associated adverse events. [46638]

Emtricitabine; Tenofovir alafenamide: (Moderate) Concurrent use of lopinavir with tenofovir alafenamide may result in elevated tenofovir serum concentrations. Tenofovir alafenamide is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. When 10 mg of tenofovir alafenamide was administered daily with lopinavir; ritonavir (800 mg/200 mg PO daily), the tenofovir C_{max} and AUC increased by 2.19-fold and 1.47-fold, respectively. Monitor for increased toxicities if these drugs are given together. [60269] [61510] [61511] [61513]

Emtricitabine; Tenofovir disoproxil fumarate: (Moderate) Caution is advised when administering tenofovir, PMPA, a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate, concurrently with inhibitors of P-gp and BCRP, such as ritonavir. Coadministration may result in increased absorption of tenofovir. Monitor for tenofovir-associated adverse reactions. [28193] [58664] (Minor) There are varying results in reports of an interaction between tenofovir and lopinavir; ritonavir. In one report, the concurrent administration of tenofovir with lopinavir; ritonavir increased tenofovir C_{max} 31%, AUC 34%, and C_{min} 29%, with slight (15%) decreases in lopinavir C_{max} and AUC; the alterations may be a food effect rather than a drug-drug interaction. In another report, lopinavir; ritonavir (400 mg; 100 mg PO twice daily for 14 days) increased the tenofovir (300 mg/day PO) C_{min} 51% and AUC 32%, with no effect seen on lopinavir; ritonavir pharmacokinetics. While the clinical significance of this interaction is unknown, and is suspected to be insignificant, patients receiving lopinavir; ritonavir with tenofovir should be monitored for tenofovir-associated adverse events. [46638]

Enalapril; Felodipine: (Moderate) Concurrent administration of felodipine with protease inhibitors may result in elevated felodipine plasma concentrations. This increase in felodipine concentration may lead to increased therapeutic and adverse effects, such as lower blood pressure, dizziness, and headache. Felodipine is metabolized by the hepatic isoenzyme CYP3A4; protease inhibitors are potent inhibitors of this enzyme. In addition, ritonavir prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. [32432] [47165]

Encainide: (Major) Concurrent administration of encainide with ritonavir may result in elevated encainide plasma concentrations. Encainide is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme and may increase serum encainide concentrations by as much as 2-fold. Because encainide has a narrow therapeutic index and adverse events may be severe, close monitoring and dose adjustment are advised if these drugs are administered together. [28315] [47165] [57084] [58664]

Encorafenib: (Major) Avoid coadministration of encorafenib and ritonavir due to increased encorafenib exposure. If concurrent use cannot be avoided, reduce the encorafenib dose to one-third of the dose used prior to the addition of ritonavir. If ritonavir is discontinued, the original encorafenib dose may be resumed after 3 to 5 elimination half-lives of ritonavir. Encorafenib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration of a strong CYP3A4 inhibitor with a single 50 mg dose of encorafenib (0.1 times the recommended dose) increased the encorafenib AUC and C_{max} by 3-fold and 68%, respectively. [47165] [63317] (Major) Avoid coadministration of lopinavir with encorafenib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Encorafenib has been associated with dose-dependent QT prolongation. [28341] [63317] [65157] [65170]

Enfortumab vedotin: (Moderate) Monitor for signs of enfortumab vedotin-related adverse reactions if coadministration with ritonavir is necessary. Concomitant use may increase free monomethyl auristatin E (MMAE) exposure, which may increase the incidence or severity of enfortumab-vedotin toxicities. MMAE, the microtubule-disrupting component of enfortumab vedotin, is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Clinical drug interaction studies have not been conducted for enfortumab vedotin. However, coadministration of another antibody-drug conjugate that contains MMAE with a strong CYP3A4 inhibitor increased the C_{max} and AUC of MMAE by 25% and 34%, respectively, with no change in the total exposure of the antibody-drug conjugate. [34557] [64845]

Entrectinib: (Major) Avoid coadministration of entrectinib with ritonavir due to increased entrectinib exposure resulting in increased treatment-related adverse effects. If coadministration cannot be avoided in adults and pediatric patients 12 years and older with BSA greater than 1.5 m², reduce the entrectinib dose to 100 mg PO once daily. If ritonavir is discontinued, resume the original entrectinib dose after 3 to 5 elimination half-lives of ritonavir. Entrectinib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration of a strong CYP3A4 inhibitor increased the AUC of entrectinib by 6-fold in a drug interaction study. [47165] [64567] (Major) Avoid coadministration of lopinavir with entrectinib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [28341] [64567] [65157] [65170]

Enzalutamide: (Severe) Coadministration of lopinavir with strong inducers of CYP3A4, such as enzalutamide, is contraindicated. Taking these drugs together could decrease lopinavir concentrations, and may lead to a reduction in antiretroviral activity. [28341] [51727] [56579] (Severe) Coadministration of ritonavir with enzalutamide is contraindicated as there is a potential for decreased ritonavir concentrations. Decreased antiretroviral concentrations may lead to a reduction of antiretroviral efficacy and the potential development of viral resistance. Ritonavir is metabolized by CYP3A4; enzalutamide is a strong CYP3A4 inducer. [47165] [51727]

Eplerenone: (Severe) Coadministration of ritonavir and eplerenone is contraindicated. Ritonavir potently inhibits the hepatic CYP3A4 isoenzyme and can increase the serum concentrations of eplerenone. Increased eplerenone concentrations may lead to a risk of developing hyperkalemia and hypotension. [27990]

Erdafitinib: (Major) Avoid coadministration of erdafitinib and ritonavir due to the risk of increased plasma concentrations of erdafitinib. If concomitant use is unavoidable, closely monitor for erdafitinib-related adverse reactions and consider dose modifications as clinically appropriate. If ritonavir is discontinued, the dose of erdafitinib may be increased in the absence of drug-related toxicity. Erdafitinib is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. The mean ratios for the C_{max} and AUC of erdafitinib were 105% and 134%, respectively, when coadministered with another strong CYP3A4 inhibitor. [47165] [64064]

Ergoloid Mesylates: (Severe) Coadministration of ergot alkaloids with potent inhibitors of CYP3A4, like anti-retroviral protease inhibitors is considered contraindicated due to the risk of acute ergot toxicity (e.g., vasospasm leading to cerebral ischemia, peripheral ischemia and/or other serious effects). Several case reports have established the clinical significance of this interaction in the medical literature. In some cases, fatal interactions have occurred. [28142] [28341] [28731] [28839] [28995] [32432] [46638] [5018] [5044] [5623] [5747] [8102]

Ergonovine: (Severe) Coadministration of ergot alkaloids with potent inhibitors of CYP3A4, like anti-retroviral protease inhibitors is considered contraindicated due to the risk of acute ergot toxicity (e.g., vasospasm leading to cerebral ischemia, peripheral ischemia and/or other serious effects). Several case reports have established the clinical significance of this interaction in the medical literature. In some cases, fatal interactions have occurred. [28142] [28341] [28731] [28839] [28995] [32432] [46638] [5018] [5044] [5623] [5747] [8102]

Ergot alkaloids: (Severe) Coadministration of ergot alkaloids with potent inhibitors of CYP3A4, like anti-retroviral protease inhibitors is considered contraindicated due to the risk of acute ergot toxicity (e.g., vasospasm leading to cerebral ischemia, peripheral ischemia and/or other serious effects). Several case reports have established the clinical significance of this interaction in the medical literature. In some cases, fatal interactions have occurred. [28142] [28341] [28731] [28839] [28995] [32432] [46638] [5018] [5044] [5623] [5747] [8102]

Ergotamine: (Severe) Coadministration of ergot alkaloids with potent inhibitors of CYP3A4, like anti-retroviral protease inhibitors is considered contraindicated due to the risk of acute ergot toxicity (e.g., vasospasm leading to cerebral ischemia, peripheral ischemia and/or other serious effects). Several case reports have established the clinical significance of this interaction in the medical literature. In some cases, fatal interactions have occurred. [28142] [28341] [28731] [28839] [28995] [32432] [46638] [5018] [5044] [5623] [5747] [8102]

Eribulin: (Major) Avoid coadministration of lopinavir with eribulin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs are associated with QT prolongation. [28341] [42449] [65157] [65170]

Erlotinib: (Major) Avoid coadministration of erlotinib with ritonavir if possible due to the increased risk of erlotinib-related adverse reactions. If concomitant use is unavoidable and severe reactions occur, reduce the dose of erlotinib by 50 mg decrements. Erlotinib is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased erlotinib exposure by 67%. [30555] [47165]

Ertugliflozin; Metformin: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Erythromycin: (Major) Avoid coadministration of lopinavir with erythromycin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Erythromycin is associated with QT prolongation and torsade de pointes (TdP). [28341] [43258] [65157] [65170] (Moderate) Caution is warranted with the

use of erythromycin and ritonavir as erythromycin may increase ritonavir serum concentrations resulting in increased treatment-related adverse effects. Erythromycin inhibits CYP3A4 and P-glycoprotein (P-gp), while ritonavir is a substrate of both CYP3A4 and P-gp. [\[47165\]](#) [\[53544\]](#)

Erythromycin; Sulfisoxazole: (Major) Avoid coadministration of lopinavir with erythromycin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Erythromycin is associated with QT prolongation and torsade de pointes (TdP). [\[28341\]](#) [\[43258\]](#) [\[65157\]](#) [\[65170\]](#) (Moderate) Caution is warranted with the use of erythromycin and ritonavir as erythromycin may increase ritonavir serum concentrations resulting in increased treatment-related adverse effects. Erythromycin inhibits CYP3A4 and P-glycoprotein (P-gp), while ritonavir is a substrate of both CYP3A4 and P-gp. [\[47165\]](#) [\[53544\]](#)

Escitalopram: (Major) Avoid coadministration of lopinavir with escitalopram due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Escitalopram has been associated with a risk of QT prolongation and torsade de pointes (TdP). [\[28270\]](#) [\[28341\]](#) [\[65157\]](#) [\[65170\]](#)

Eslicarbazepine: (Major) Concurrent administration of eslicarbazepine with ritonavir may result in decreased plasma concentrations of ritonavir. Eslicarbazepine is an inducer of the hepatic isoenzyme CYP3A4; ritonavir is metabolized by this enzyme. Caution and close monitoring for decreased antiviral efficacy are advised if these drugs are administered together. [\[56436\]](#) [\[58664\]](#)

Esmolol: (Moderate) Ritonavir is expected to decrease the hepatic CYP metabolism of beta-blockers, resulting in increased beta-blocker concentrations. Cardiac and neurologic events have been reported when ritonavir is concurrently administered with beta-blockers. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including beta-blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased beta-blocker doses may be warranted. [\[5044\]](#)

Esomeprazole: (Moderate) Concurrent administration of esomeprazole with ritonavir may result in elevated esomeprazole plasma concentrations. Esomeprazole is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Monitor patients for increased side effects if these drugs are administered together. [\[58664\]](#) [\[6265\]](#)

Esomeprazole; Naproxen: (Moderate) Concurrent administration of esomeprazole with ritonavir may result in elevated esomeprazole plasma concentrations. Esomeprazole is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Monitor patients for increased side effects if these drugs are administered together. [\[58664\]](#) [\[6265\]](#)

Estazolam: (Moderate) In vitro studies with human liver microsomes indicate that the biotransformation of estazolam to the major circulating metabolite 4-hydroxy-estazolam is mediated by CYP3A. In theory, CYP3A4 inhibitors, such as protease inhibitors, may reduce the metabolism of estazolam and increase the potential for benzodiazepine toxicity (i.e., prolonged sedation and respiratory depression) [\[30413\]](#) [\[32432\]](#) [\[46638\]](#)

Esterified Estrogens: (Moderate) Ritonavir has been shown to increase the metabolism of ethinyl estradiol; a similar interaction may occur with other estrogens used for hormone replacement therapy. Patients should report any breakthrough bleeding or adverse events to their prescribers. [\[28315\]](#) [\[28341\]](#)

Esterified Estrogens; Methyltestosterone: (Moderate) Ritonavir has been shown to increase the metabolism of ethinyl estradiol; a similar interaction may occur with other estrogens used for hormone replacement therapy. Patients should report any breakthrough bleeding or adverse events to their prescribers. [\[28315\]](#) [\[28341\]](#)

Estradiol Cypionate; Medroxyprogesterone: (Major) Coadministration of medroxyprogesterone, a CYP3A substrate with ritonavir, a strong CYP3A inhibitor should be avoided since it is expected to increase concentrations of medroxyprogesterone acetate. Formal drug interaction studies have not been conducted; however, medroxyprogesterone is metabolized primarily by hydroxylation via the CYP3A4 in vitro. [\[28380\]](#) [\[34557\]](#) [\[47165\]](#) [\[57648\]](#) (Moderate) Ritonavir has been shown to increase the metabolism of ethinyl estradiol. Ritonavir is a substrate and inhibitor of CYP3A4. It is not known if the effects of protease inhibitors are similar on estradiol; however, estradiol is metabolized by CYP3A4, similar to ethinyl estradiol. [\[28315\]](#)

Estradiol: (Moderate) Ritonavir has been shown to increase the metabolism of ethinyl estradiol. Ritonavir is a substrate and inhibitor of CYP3A4. It is not known if the effects of protease inhibitors are similar on estradiol; however, estradiol is metabolized by CYP3A4, similar to ethinyl estradiol. [\[28315\]](#)

Estradiol; Levonorgestrel: (Major) Data on the effects that protease inhibitors have on the serum concentrations of estrogens and progestins are complex. Some protease inhibitors increase (i.e., ritonavir, lopinavir; ritonavir, nelfinavir, tipranavir) and others decrease (i.e., atazanavir, indinavir) the metabolism of hormonal contraceptives. The safety and efficacy of hormonal contraceptives may be affected if coadministered with protease inhibitors. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors concurrently should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with protease inhibitors to use an additional method of contraception to protect against unwanted pregnancy, unless other drug-specific recommendations are made by the manufacturer of the protease inhibitor. Furthermore, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with protease inhibitors should use an additional barrier method of contraception such as condoms. [\[46638\]](#) [\[5044\]](#) (Moderate) Ritonavir has been shown to increase the metabolism of ethinyl estradiol. Ritonavir is a substrate and inhibitor of CYP3A4. It is not known if the effects of protease inhibitors are similar on estradiol; however, estradiol is metabolized by CYP3A4, similar to ethinyl estradiol. [\[28315\]](#)

Estradiol; Norethindrone: (Moderate) Many anti-retroviral protease inhibitors may interact with hormonal agents like norethindrone, due to their actions on CYP metabolism, particularly CYP3A4. Data on the effects that protease inhibitors have on the serum concentrations of norethindrone are complex and are based mostly off of data with norethindrone-containing contraceptives. For example, ritonavir (also

found in combinations like lopinavir; ritonavir, and used as a booster in many HIV treatment regimens) may decrease the metabolism of norethindrone, raising norethindrone concentrations. Women receiving norethindrone for hormone replacement or contraception should report potential hormonal adverse effects (e.g., bleeding pattern changes, acne, emotional lability) or any changes in efficacy (e.g., noted changes in bleeding patterns) to their prescribers. Because norethindrone-containing contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive norethindrone contraception concurrently with ritonavir should use an additional barrier method of contraception such as condoms. [58679] [7731] (Moderate) Ritonavir has been shown to increase the metabolism of ethinyl estradiol. Ritonavir is a substrate and inhibitor of CYP3A4. It is not known if the effects of protease inhibitors are similar on estradiol; however, estradiol is metabolized by CYP3A4, similar to ethinyl estradiol. [28315]

Estradiol; Norgestimate: (Moderate) Ritonavir has been shown to increase the metabolism of ethinyl estradiol. Ritonavir is a substrate and inhibitor of CYP3A4. It is not known if the effects of protease inhibitors are similar on estradiol; however, estradiol is metabolized by CYP3A4, similar to ethinyl estradiol. [28315]

Estradiol; Progesterone: (Moderate) Ritonavir has been shown to increase the metabolism of ethinyl estradiol. Ritonavir is a substrate and inhibitor of CYP3A4. It is not known if the effects of protease inhibitors are similar on estradiol; however, estradiol is metabolized by CYP3A4, similar to ethinyl estradiol. [28315]

Estropipate: (Moderate) Ritonavir has been shown to increase the metabolism of ethinyl estradiol; a similar interaction may occur with other estrogens used for hormone replacement therapy. Patients should report any breakthrough bleeding or adverse events to their prescribers. [5044] [5070]

Eszopiclone: (Major) The adult dose of eszopiclone should not exceed 2 mg/day during co-administration of potent CYP3A4 inhibitors, such as anti-retroviral protease inhibitors. CYP3A4 is a primary metabolic pathway for eszopiclone, and increased systemic exposure to eszopiclone increases the risk of next-day psychomotor or memory impairment, which may decrease the ability to perform tasks requiring full mental alertness such as driving. [30571] [31320]

Ethanol: (Major) Concurrent administration of ethanol with ritonavir may result in decreased plasma concentrations of ritonavir, which may affect antiviral efficacy. Ethanol is an inducer of the hepatic isoenzyme CYP3A4; ritonavir is a substrate of this enzyme. Caution and close monitoring are advised if ethanol and ritonavir are administered together. [34760] [34761] [34762] [58664]

Ethinyl Estradiol: (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and C_{max} by 32%. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [46638] [5044]

Ethinyl Estradiol; Desogestrel: (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and C_{max} by 32%. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [46638] [5044]

Ethinyl Estradiol; Ethynodiol Diacetate: (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and C_{max} by 32%. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [46638] [5044]

Ethinyl Estradiol; Etonogestrel: (Major) Coadministration may result in an increased or decreased effect of etonogestrel. Contraceptive efficacy may be reduced. Etonogestrel is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor and CYP3A4 inducer. [41597] [46375] [47165] (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and C_{max} by 32%. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [46638] [5044]

Ethinyl Estradiol; Levonorgestrel: (Major) Data on the effects that protease inhibitors have on the serum concentrations of estrogens and progestins are complex. Some protease inhibitors increase (i.e., ritonavir, lopinavir; ritonavir, nelfinavir, tipranavir) and others decrease (i.e., atazanavir, indinavir) the metabolism of hormonal contraceptives. The safety and efficacy of hormonal contraceptives may be affected if coadministered with protease inhibitors. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors concurrently should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with protease inhibitors to use an additional method of contraception to protect against unwanted pregnancy, unless other drug-specific recommendations are made by the manufacturer of the protease inhibitor. Furthermore, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with protease inhibitors should use an additional barrier method of contraception such as condoms. [46638] [5044] (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and C_{max} by 32%. Women receiving hormonal

contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [46638] [5044]

Ethinyl Estradiol; Levonorgestrel; Ferrous bisglycinate: (Major) Data on the effects that protease inhibitors have on the serum concentrations of estrogens and progestins are complex. Some protease inhibitors increase (i.e., ritonavir, lopinavir; ritonavir, nelfinavir, tipranavir) and others decrease (i.e., atazanavir, indinavir) the metabolism of hormonal contraceptives. The safety and efficacy of hormonal contraceptives may be affected if coadministered with protease inhibitors. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors concurrently should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with protease inhibitors to use an additional method of contraception to protect against unwanted pregnancy, unless other drug-specific recommendations are made by the manufacturer of the protease inhibitor. Furthermore, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with protease inhibitors should use an additional barrier method of contraception such as condoms. [46638] [5044] (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and Cmax by 32%. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [46638] [5044]

Ethinyl Estradiol; Levonorgestrel; Folic Acid; Levomefolate: (Major) Data on the effects that protease inhibitors have on the serum concentrations of estrogens and progestins are complex. Some protease inhibitors increase (i.e., ritonavir, lopinavir; ritonavir, nelfinavir, tipranavir) and others decrease (i.e., atazanavir, indinavir) the metabolism of hormonal contraceptives. The safety and efficacy of hormonal contraceptives may be affected if coadministered with protease inhibitors. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors concurrently should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with protease inhibitors to use an additional method of contraception to protect against unwanted pregnancy, unless other drug-specific recommendations are made by the manufacturer of the protease inhibitor. Furthermore, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with protease inhibitors should use an additional barrier method of contraception such as condoms. [46638] [5044] (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and Cmax by 32%. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [46638] [5044]

Ethinyl Estradiol; Norelgestromin: (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and Cmax by 32%. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [46638] [5044]

Ethinyl Estradiol; Norethindrone Acetate: (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and Cmax by 32%. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [46638] [5044] (Moderate) Many anti-retroviral protease inhibitors may interact with hormonal agents like norethindrone, due to their actions on CYP metabolism, particularly CYP3A4. Data on the effects that protease inhibitors have on the serum concentrations of norethindrone are complex and are based mostly off of data with norethindrone-containing contraceptives. For example, ritonavir (also found in combinations like lopinavir; ritonavir, and used as a booster in many HIV treatment regimens) may decrease the metabolism of norethindrone, raising norethindrone concentrations. Women receiving norethindrone for hormone replacement or contraception should report potential hormonal adverse effects (e.g., bleeding pattern changes, acne, emotional lability) or any changes in efficacy (e.g., noted changes in bleeding patterns) to their prescribers. Because norethindrone-containing contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive norethindrone contraception concurrently with ritonavir should use an additional barrier method of contraception such as condoms. [58679] [7731]

Ethinyl Estradiol; Norethindrone Acetate; Ferrous fumarate: (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and Cmax by 32%. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [46638] [5044]

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Ethinyl Estradiol; Norgestimate: (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and Cmax by 32%. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [46638] [5044]

Ethinyl Estradiol; Norgestrel: (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and Cmax by 32%. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [46638] [5044]

Ethosuximide: (Moderate) Ritonavir decreases the hepatic CYP metabolism of ethosuximide, resulting in increased ethosuximide concentrations. If coadministration is warranted, do so with caution and careful monitoring of ethosuximide concentrations. A 50% dose reduction of ethosuximide may be needed. [27896] [28001] [28315] [46638]

Ethotoin: (Major) Concurrent use of ritonavir with ethotoin, phenytoin, or fosphenytoin should be avoided when possible. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. Additionally, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [28315] [46638]

Etonogestrel: (Major) Coadministration may result in an increased or decreased effect of etonogestrel. Contraceptive efficacy may be reduced. Etonogestrel is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor and CYP3A4 inducer. [41597] [46375] [47165]

Etravirine: (Moderate) Concomitant use of etravirine with full-dose ritonavir (i.e., 600 mg twice daily) may cause a significant decrease in etravirine plasma concentration and, thus, a loss of therapeutic effect. Etravirine and full-dose ritonavir should not be coadministered. [\[33718\]](#)

Everolimus: (Major) Avoid coadministration of ritonavir with everolimus (Afinitor; Afinitor Disperz) due to increased plasma concentrations of everolimus. Coadministration of ritonavir with everolimus (Zortress) is not recommended without close monitoring of everolimus whole blood trough concentrations. Everolimus is a CYP3A4 substrate as well as a substrate of P-glycoprotein (P-gp); ritonavir is a strong inhibitor of CYP3A4 and a P-gp inhibitor. Coadministration with another strong CYP3A4/P-gp inhibitor increased everolimus exposure by 15-fold. [\[28380\]](#) [\[34557\]](#) [\[47165\]](#) [\[49598\]](#) [\[49823\]](#)

Ezetimibe; Simvastatin: (Severe) The coadministration of anti-retroviral protease inhibitors with simvastatin is contraindicated. Taking these drugs together may significantly increase the serum concentration of simvastatin; thereby increasing the risk of myopathy and rhabdomyolysis. One report has demonstrated that ritonavir plus saquinavir therapy markedly increases the AUC for simvastatin by 3059%. Simvastatin is a substrate for CYP3A4 and the drug transporter organic anion transporting polypeptide (OATP1B1); protease inhibitors are CYP3A4 and OATP inhibitors. [\[28605\]](#) [\[39682\]](#) [\[46638\]](#) [\[61510\]](#) [\[61511\]](#) [\[61512\]](#) [\[61513\]](#)

Ezogabine: (Major) Avoid coadministration of lopinavir with ezogabine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [\[28341\]](#) [\[44800\]](#) [\[65157\]](#) [\[65170\]](#)

Fedratinib: (Major) Avoid coadministration of fedratinib with ritonavir as concurrent use may increase fedratinib exposure. If concurrent use cannot be avoided, reduce the dose of fedratinib to 200 mg PO once daily. If ritonavir is discontinued, increase the fedratinib dose as follows: 300 mg PO once daily for 2 weeks and then 400 mg PO once daily thereafter as tolerated. Fedratinib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration of another strong CYP3A4 inhibitor increased fedratinib exposure by 3-fold. [\[28315\]](#) [\[64568\]](#)

Felbamate: (Major) Concurrent administration of felbamate with ritonavir may result in decreased plasma concentrations of ritonavir. Felbamate is a mild inducer of the hepatic isoenzyme CYP3A4; ritonavir is metabolized by this enzyme. Monitor for antiviral efficacy if these drugs are administered together. [\[4190\]](#) [\[58664\]](#)

Felodipine: (Moderate) Concurrent administration of felodipine with protease inhibitors may result in elevated felodipine plasma concentrations. This increase in felodipine concentration may lead to increased therapeutic and adverse effects, such as lower blood pressure, dizziness, and headache. Felodipine is metabolized by the hepatic isoenzyme CYP3A4; protease inhibitors are potent inhibitors of this enzyme. In addition, ritonavir prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. [\[32432\]](#) [\[47165\]](#)

Fentanyl: (Major) Consider a reduced dose of fentanyl with frequent monitoring for respiratory depression and sedation if concurrent use of ritonavir is necessary. If ritonavir is discontinued, consider increasing the fentanyl dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Fentanyl is a CYP3A4 substrate, and coadministration with CYP3A4 inhibitors like ritonavir can increase fentanyl exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of fentanyl. If ritonavir is discontinued, fentanyl plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to fentanyl. Clinical investigations have suggested that ritonavir may decrease the clearance of fentanyl by 67%, increase the elimination half-life from 9.4 to 20.1 hours, and increase the systemic exposure of fentanyl by 174% (range: 52 to 420%). [\[26403\]](#) [\[29623\]](#) [\[29763\]](#) [\[32731\]](#) [\[40943\]](#) [\[47165\]](#)

Fesoterodine: (Moderate) Fesoterodine is rapidly hydrolyzed to its active metabolite, 5-hydroxymethyltolterodine, which is metabolized via hepatic CYP3A4 and 2D6. In theory, the CYP3A4 inhibitory effects of anti-retroviral protease inhibitors may result in an increase in plasma concentrations of 5-hydroxymethyltolterodine. Anti-retroviral protease inhibitors which also inhibit 2D6, such as ritonavir, may impair both CYP metabolic pathways of 5-hydroxymethyltolterodine. Fesoterodine doses greater than 4 mg/day are not recommended during concurrent use of potent 3A4 inhibitors. [\[11397\]](#)

Fexofenadine: (Minor) The plasma concentrations of fexofenadine may be elevated when administered concurrently with ritonavir. Clinical monitoring for adverse effects, such as drowsiness, is recommended during coadministration. Ritonavir is a P-glycoprotein (P-gp) inhibitor, while fexofenadine is a P-gp substrate. [\[28380\]](#) [\[34526\]](#) [\[34527\]](#) [\[47165\]](#)

Fexofenadine; Pseudoephedrine: (Minor) The plasma concentrations of fexofenadine may be elevated when administered concurrently with ritonavir. Clinical monitoring for adverse effects, such as drowsiness, is recommended during coadministration. Ritonavir is a P-glycoprotein (P-gp) inhibitor, while fexofenadine is a P-gp substrate. [\[28380\]](#) [\[34526\]](#) [\[34527\]](#) [\[47165\]](#)

Fingolimod: (Major) If possible, avoid coadministration of lopinavir; ritonavir and fingolimod. If concomitant use cannot be avoided, overnight monitoring with continuous ECG in a medical facility after the first fingolimod dose is advised. Fingolimod has not been studied in patients treated with drugs that prolong the QT interval, but drugs that prolong the QT interval have been associated with cases of torsade de pointes in patients with bradycardia. Lopinavir; ritonavir is associated with a possible risk for QT prolongation and torsade de pointes (TdP) based on varying levels of documentation. Fingolimod initiation results in decreased heart rate and may prolong the QT interval. Fingolimod is contraindicated for use by patients with a baseline QTc interval \geq 500 msec. [\[28341\]](#) [\[41823\]](#)

Flecainide: (Major) Concurrent use of HIV treatment doses of ritonavir with flecainide is contraindicated. Cautious consideration may be given to administering amiodarone with boosting doses of ritonavir. The potential increase in plasma concentrations of flecainide could result in significant adverse effects. [\[47165\]](#) (Major) Due to the potential for QT prolongation and torsade de pointes (TdP), caution is advised when administering lopinavir; ritonavir with flecainide. Lopinavir; ritonavir is associated with QT prolongation. Flecainide is a Class IC antiarrhythmic associated with a possible risk for QT prolongation and/or TdP; flecainide increases the QT interval, but largely

due to prolongation of the QRS interval. Although causality for TdP has not been established for flecainide, patients receiving concurrent drugs which have the potential for QT prolongation may have an increased risk of developing proarrhythmias. [23774] [28341] [28752]

Flibanserin: (Severe) The concomitant use of flibanserin and strong CYP3A4 inhibitors, such as ritonavir, is contraindicated. Strong CYP3A4 inhibitors can increase flibanserin concentrations, which can cause severe hypotension and syncope. If initiating flibanserin following use of a strong CYP3A4 inhibitor, start flibanserin at least 2 weeks after the last dose of the CYP3A4 inhibitor. If initiating a strong CYP3A4 inhibitor following flibanserin use, start the strong CYP3A4 inhibitor at least 2 days after the last dose of flibanserin. [60099]

Fluconazole: (Major) Avoid coadministration of lopinavir with fluconazole due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Fluconazole has been associated with QT prolongation and rare cases of torsade de pointes (TdP). Based on metabolic profiles, clinically significant pharmacokinetic drug interactions are not expected. [28341] [28674] [65157] [65170] (Moderate) Caution is warranted with the use of fluconazole and ritonavir as ritonavir serum concentrations may be increased resulting in increased treatment-related adverse effects. Fluconazole is a moderate CYP3A4 inhibitor, while ritonavir is a substrate of CYP3A4. [28315] [28674]

Fluoxetine: (Major) Avoid coadministration of lopinavir with fluoxetine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. QT prolongation and torsade de pointes (TdP) have been reported in patients treated with fluoxetine. [28341] [65157] [65170] (Moderate) A dose reduction of fluoxetine may be necessary if coadministered with ritonavir. Increased fluoxetine exposure may occur. Cardiac and neurologic events have been reported when ritonavir has been administered with fluoxetine. [47165]

Fluoxetine; Olanzapine: (Major) Avoid coadministration of lopinavir with fluoxetine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. QT prolongation and torsade de pointes (TdP) have been reported in patients treated with fluoxetine. [28341] [65157] [65170] (Major) Avoid coadministration of lopinavir with olanzapine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Limited data, including some case reports, suggest that olanzapine may be associated with a significant prolongation of the QTc interval. [28341] [28785] [32732] [32734] [32745] [32746] [65157] [65170] (Moderate) A dose reduction of fluoxetine may be necessary if coadministered with ritonavir. Increased fluoxetine exposure may occur. Cardiac and neurologic events have been reported when ritonavir has been administered with fluoxetine. [47165] (Moderate) Ritonavir may reduce olanzapine serum concentrations by approximately 50%; how this affects olanzapine efficacy, however, is not known. Ritonavir appears to induce olanzapine's metabolism by either CYP1A2 or glucuronide conjugation. If ritonavir and olanzapine are used concurrently, monitor for reduced olanzapine effect and adjust olanzapine dose as needed. [27275]

Fluphenazine: (Major) Avoid coadministration of lopinavir with fluphenazine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Fluphenazine is associated with a possible risk for QT prolongation. [28341] [28415] [65157] [65170]

Flurazepam: (Major) CYP3A4 inhibitors, such as protease inhibitors, may reduce the metabolism of flurazepam and increase the potential for benzodiazepine toxicity. A decrease in the flurazepam dose may be needed. [28001] [28345] [32432]

Fluticasone: (Major) Coadministration of inhaled fluticasone propionate and ritonavir is not recommended; use caution with inhaled fluticasone furoate. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving inhaled fluticasone propionate with ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Fluticasone is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. In a drug interaction study, coadministration with ritonavir increased plasma fluticasone propionate exposure resulting in an 86% decrease in serum cortisol AUC. Another strong inhibitor increased fluticasone furoate exposure by 1.33-fold with a 27% reduction in weighted mean serum cortisol; this change does not necessitate dose adjustment of fluticasone furoate. [40360] [40475] [43972] [57805]

Fluticasone; Salmeterol: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28318] [28341] [32901] [33925] [41231] [65157] [65170] (Major) Avoid coadministration of salmeterol with ritonavir. The coadministration of salmeterol with CYP3A4 inhibitors can result in elevated salmeterol plasma concentrations and increased risk for adverse reactions, particularly cardiovascular effects. [28315] [28467] [47165] (Major) Coadministration of inhaled fluticasone propionate and ritonavir is not recommended; use caution with inhaled fluticasone furoate. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving inhaled fluticasone propionate with ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Fluticasone is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. In a drug interaction study, coadministration with ritonavir increased plasma fluticasone propionate exposure resulting in an 86% decrease in serum cortisol AUC. Another strong inhibitor increased fluticasone furoate exposure by 1.33-fold with a 27% reduction in weighted mean serum cortisol; this change does not necessitate dose adjustment of fluticasone furoate. [40360] [40475] [43972] [57805]

Fluticasone; Umeclidinium; Vilanterol: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more

clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28318] [28341] [32901] [33925] [41231] [65157] [65170] (Major) Coadministration of inhaled fluticasone propionate and ritonavir is not recommended; use caution with inhaled fluticasone furoate. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving inhaled fluticasone propionate with ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Fluticasone is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. In a drug interaction study, coadministration with ritonavir increased plasma fluticasone propionate exposure resulting in an 86% decrease in serum cortisol AUC. Another strong inhibitor increased fluticasone furoate exposure by 1.33-fold with a 27% reduction in weighted mean serum cortisol; this change does not necessitate dose adjustment of fluticasone furoate. [40360] [40475] [43972] [57805]

Fluticasone; Vilanterol: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28318] [28341] [32901] [33925] [41231] [65157] [65170] (Major) Coadministration of inhaled fluticasone propionate and ritonavir is not recommended; use caution with inhaled fluticasone furoate. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving inhaled fluticasone propionate with ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Fluticasone is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. In a drug interaction study, coadministration with ritonavir increased plasma fluticasone propionate exposure resulting in an 86% decrease in serum cortisol AUC. Another strong inhibitor increased fluticasone furoate exposure by 1.33-fold with a 27% reduction in weighted mean serum cortisol; this change does not necessitate dose adjustment of fluticasone furoate. [40360] [40475] [43972] [57805]

Fluvastatin: (Moderate) Ritonavir is an inhibitor of CYP3A4 and may increase exposure to drugs metabolized by this enzyme, such as fluvastatin. Because fluvastatin does not rely exclusively on CYP3A4 for its metabolism (approximately 20%), ritonavir may not interact to the same extent as expected with other HMG-CoA reductase inhibitors. Elevated serum concentrations of fluvastatin may increase the risk for adverse reactions, such as myopathy. [28774] [45527] [58664]

Fluvoxamine: (Major) Avoid coadministration of lopinavir with fluvoxamine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. QT prolongation and torsade de pointes (TdP) has been reported with postmarketing use of fluvoxamine. [28341] [50507] [65157] [65170] (Moderate) Concurrent administration of fluvoxamine with ritonavir may result in increased plasma concentrations of one or both drugs. Fluvoxamine is partially metabolized by CYP2D6 and ritonavir is a weak CYP2D6 inhibitor. In addition, ritonavir is metabolized by CYP3A4, and fluvoxamine is a moderate CYP3A4 inhibitor. Caution and close monitoring are advised if these drugs are administered together. [47165] [50507]

Food: (Moderate) The pharmacokinetic parameters of anti-retroviral medications (anti-retroviral non-nucleoside reverse transcriptase inhibitors (NNRTIs), anti-retroviral nucleoside reverse transcriptase inhibitors (NRTIs), anti-retroviral nucleotide reverse transcriptase inhibitors, and anti-retroviral protease inhibitors) metabolized through the CYP isoenzyme system are slightly altered by smoked and oral marijuana. Despite this interaction, marijuana is not expected to adversely affect anti-retroviral efficacy. However, the incidence of marijuana associated adverse effects may change following coadministration with anti-retroviral drugs. Many anti-retrovirals are inhibitors of CYP3A4, an isoenzyme partially responsible for the metabolism of marijuana's most psychoactive compound, delta-9-tetrahydrocannabinol (Delta-9-THC). When given concurrently with anti-retrovirals, the amount of Delta-9-THC converted to the active metabolite 11-hydroxy-delta-9-tetrahydrocannabinol (11-OH-THC) may be reduced. These changes in Delta-9-THC and 11-OH-THC plasma concentrations may result in an altered marijuana adverse event profile. [42135] [42294] [42448]

Formoterol: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28318] [28341] [32901] [33925] [41231] [65157] [65170]

Formoterol; Mometasone: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28318] [28341] [32901] [33925] [41231] [65157] [65170] (Moderate) Coadministration of mometasone with ritonavir (a strong CYP3A4 inhibitor) may cause mometasone serum concentrations to increase, potentially resulting in Cushing's syndrome and adrenal suppression. Consider use of an alternative corticosteroid whose concentrations are less affected by strong CYP3A4 inhibitors, such as beclomethasone and prednisolone, especially during long-term treatment. [28341] [47165] [58620]

Fosamprenavir: (Major) The coadministration of fosamprenavir (twice daily, boosted with ritonavir) and lopinavir; ritonavir tablets (400/100 mg) resulted in altered pharmacokinetics of both drugs in addition to an increased rate of adverse events. Decreases were seen in the fosamprenavir C_{max} (by 58%), AUC (by 63%), and C_{min} (by 65%). Increases were seen in the lopinavir; ritonavir (400/100 mg) C_{max} (by 30%), AUC (by 37%), and C_{min} (by 52%). The coadministration of fosamprenavir (1400 mg twice daily) and lopinavir; ritonavir (533/133 mg twice daily) resulted in decreased fosamprenavir C_{max} (by 13%), AUC (by 26%), and C_{min} (by 42%), in addition to an increased rate of adverse events. With respect to safety and efficacy, appropriate doses of fosamprenavir and lopinavir; ritonavir, when used in combination, have not been established. [28341] [29012] [46638]

Foscarnet: (Major) Avoid coadministration of lopinavir with foscarnet due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Both QT prolongation and torsade de pointes (TdP) have been reported during postmarketing use of foscarnet. [28341] [28377] [65157] [65170] (Moderate) Abnormal renal function has been observed in clinical practice during the use of foscarnet in combination with ritonavir. If these drugs are administered together, monitor kidney function. [28377] [47165]

Fosphenytoin: (Major) Concurrent use of ritonavir with ethosuximide, phenytoin, or fosphenytoin should be avoided when possible. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. Additionally, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [28315] [46638]

Fostamatinib: (Moderate) Monitor for fostamatinib toxicities that may require fostamatinib dose reduction (i.e., elevated hepatic enzymes, neutropenia, high blood pressure, severe diarrhea) if given concurrently with a strong CYP3A4 inhibitor. Concomitant use of fostamatinib with a strong CYP3A4 inhibitor increases exposure to the major active metabolite, R406, which may increase the risk of adverse reactions. R406 is extensively metabolized by CYP3A4; ritonavir is a strong CYP3A4 inhibitor. Coadministration of fostamatinib with another strong CYP3A4 inhibitor increased R406 AUC by 102% and C_{max} by 37%. [47165] [63084]

Galantamine: (Moderate) The plasma concentrations of galantamine, a partial CYP3A4 substrate, may be elevated when administered with protease inhibitors, which are strong CYP3A4 inhibitors. If this combination is required, monitor for galantamine-related adverse effects such as nausea, vomiting, diarrhea, increased urination, decreased appetite, confusion, dizziness, bradycardia, and excessive sweating. [62457]

Gefitinib: (Moderate) Monitor for an increase in gefitinib-related adverse reactions if coadministration with ritonavir is necessary. Gefitinib is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased gefitinib exposure by 80%. [28341] [45935] [47165] [56579]

Gemifloxacin: (Major) Avoid coadministration of lopinavir with gemifloxacin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Gemifloxacin may prolong the QT interval in some patients. The maximal change in the QTc interval occurs approximately 5 to 10 hours following oral administration of gemifloxacin. [28341] [28419] [28420] [28424] [65157] [65170]

Gemtuzumab Ozogamicin: (Major) Avoid coadministration of lopinavir with gemtuzumab due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Although QT interval prolongation has not been reported with gemtuzumab, it has been reported with other drugs that contain calicheamicin. [28341] [62292] [65157] [65170]

Gilteritinib: (Major) Avoid coadministration of lopinavir with gilteritinib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Both drugs have been associated with QT prolongation. [28341] [63787] [65157] [65170] (Major) Consider an alternative to ritonavir during treatment with gilteritinib. Concurrent use may increase gilteritinib exposure resulting in treatment-related adverse events. If coadministration is required, frequently monitor for gilteritinib adverse reactions. Interrupt therapy and reduce the gilteritinib dose if serious or life-threatening toxicity occurs. Gilteritinib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration of a strong CYP3A4 inhibitor increased the gilteritinib AUC by 120% in a drug interaction study. [47165] [63787]

Glasdegib: (Major) Avoid coadministration of lopinavir with glasdegib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Glasdegib therapy may result in QT prolongation and ventricular arrhythmias including ventricular fibrillation and ventricular tachycardia. [28341] [63777] [65157] [65170] (Major) Consider an alternative to ritonavir during treatment with glasdegib. Concurrent use may increase glasdegib exposure resulting in treatment-related adverse events including QT prolongation. If coadministration cannot be avoided, monitor for increased adverse events; more frequent ECG monitoring is recommended. Glasdegib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration of a strong CYP3A4 inhibitor increased the glasdegib AUC by 2.4-fold in a drug interaction study. [47165] [63777]

Glecaprevir; Pibrentasvir: (Major) Coadministration of glecaprevir with lopinavir is not recommended as coadministration may increase serum concentrations of glecaprevir and increase the risk of adverse effects. Glecaprevir is a substrate of CYP3A4, P-glycoprotein (P-gp), and OATP1B1; lopinavir; ritonavir is an inhibitor of CYP3A4, P-gp, and OATP1B1. In drug interaction studies, coadministration of lopinavir; ritonavir with glecaprevir; pibrentasvir resulted in an approximately 4-fold increase in the AUC of glecaprevir. [28341] [56579] [62201] (Major) Coadministration of glecaprevir with ritonavir is not recommended as coadministration may increase serum concentrations of glecaprevir and increase the risk of adverse effects. Glecaprevir is a substrate of CYP3A4 and P-glycoprotein (P-gp); ritonavir is an inhibitor of CYP3A4 and P-gp. Additionally, ritonavir is a P-gp substrate and glecaprevir is a P-gp inhibitor; concentrations of ritonavir may also be increased. [28380] [34557] [62201] (Major) Coadministration of pibrentasvir with ritonavir is not recommended as coadministration may increase serum concentrations of pibrentasvir and increase the risk of adverse effects. Pibrentasvir is a substrate of the drug transporter P-glycoprotein (P-gp); ritonavir is an inhibitor of P-gp. Additionally, ritonavir is a P-gp substrate and pibrentasvir is a P-gp inhibitor; concentrations of ritonavir may also be increased. [28380] [34557] [62201]

Glipizide; Metformin: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease

inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Glyburide; Metformin: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Glycopyrrolate; Formoterol: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28318] [28341] [32901] [33925] [41231] [65157] [65170]

Goserelin: (Major) Avoid coadministration of lopinavir with goserelin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Androgen deprivation therapy (i.e., goserelin) may prolong the QT/QTc interval. [28341] [28592] [65157] [65170]

Granisetron: (Major) Avoid coadministration of lopinavir with granisetron due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [28341] [31723] [65157] [65170] (Minor) Plasma concentrations of granisetron may be elevated when administered concurrently with ritonavir. Clinical monitoring for adverse effects, such as gastrointestinal or CNS effects, is recommended during coadministration. Ritonavir is a CYP3A4 inhibitor; granisetron is a CYP3A4 substrate. [28315] [31723] [47165]

Grapefruit juice: (Moderate) Concurrent administration of ritonavir with grapefruit juice may result in elevated ritonavir concentrations. Grapefruit juice is an inhibitor of the hepatic isoenzymes CYP3A4 and CYP2D6, and an inhibitor of the drug transporter P-glycoprotein (P-gp). Ritonavir is metabolized by both enzymes and is a substrate for P-gp. Caution and close monitoring are advised if these drugs are administered together. [58664]

Guaifenesin; Hydrocodone: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531]

Guaifenesin; Hydrocodone; Pseudoephedrine: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531]

Guanfacine: (Major) Ritonavir may significantly alter guanfacine plasma concentrations. Guanfacine is primarily metabolized by CYP3A4. Ritonavir is a potent CYP3A4 inhibitor; moderate CYP3A4 induction has been reported with concomitant use of voriconazole. The net effect of this potential interaction is unclear, but guanfacine dosage adjustments, most likely a dose decrease, may be required. FDA-approved labeling for extended-release (ER) guanfacine recommends that, if used with a moderate to strong CYP3A4 inhibitor, the guanfacine dosage should be decreased to half of the recommended dose and the patient should be closely monitored for alpha-adrenergic effects (e.g., hypotension, drowsiness, bradycardia). However, if used with a moderate to strong CYP3A4 inducer, labeling recommends to consider doubling the recommended dose of guanfacine ER; if the inducer is added in a patient already receiving guanfacine, this escalation should occur over 1 to 2 weeks. If the inducer or inhibitor is discontinued, guanfacine ER should return to its recommended dose (with downward titration occurring over 1 to 2 weeks). Specific recommendations for immediate-release (IR) guanfacine are not available. [27493] [43566] [47165]

Halofantrine: (Moderate) Protease Inhibitors significantly inhibit cytochrome CYP3A4, and may lead to an inhibition of halofantrine metabolism, placing the patient at risk for halofantrine cardiac toxicity. [4718] [4968]

Halogenated Anesthetics: (Major) Avoid coadministration of lopinavir with halogenated anesthetics due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir and halogenated anesthetics can both prolong the QT interval. [28341] [28457] [28458] [28754] [28755] [28756] [65157] [65170]

Haloperidol: (Major) Avoid coadministration of lopinavir with haloperidol due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. QT

prolongation and torsade de pointes (TdP) have been observed during haloperidol treatment. Excessive doses (particularly in the overdose setting) or IV administration of haloperidol may be associated with a higher risk of QT prolongation. [23500] [23779] [28307] [28341] [28415] [65157] [65170] (Moderate) Mild to moderate increases in haloperidol plasma concentrations have been reported during concurrent use of haloperidol and inhibitors of CYP3A4 or CYP2D6, such as ritonavir. Elevated haloperidol concentrations may increase the risk of adverse effects. Closely monitor for adverse events when these medications are coadministered. [28307] [47165]

Histrelin: (Major) Avoid coadministration of lopinavir with histrelin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Androgen deprivation therapy (i.e., histrelin) may prolong the QT/QTc interval. [28341] [30369] [65157] [65170]

Homatropine; Hydrocodone: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531]

Hydantoins: (Major) Concurrent use of lopinavir; ritonavir and hydantoins should be avoided when possible. Coadministration results in decreased plasma concentrations of lopinavir, ritonavir, and the hydantoin. Additionally, once daily regimens of lopinavir; ritonavir should not be administered with phenytoin due to hepatic enzyme induction by phenytoin. [28341] [46638] (Major) Concurrent use of ritonavir with ethosin, phenytoin, or fosphenytoin should be avoided when possible. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. Additionally, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [28315] [46638]

Hydrochlorothiazide, HCTZ; Losartan: (Moderate) Concurrent administration of losartan with ritonavir may result in elevated losartan plasma concentrations. Losartan is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [47165] [5339] [58664]

Hydrochlorothiazide, HCTZ; Metoprolol: (Moderate) Metoprolol is significantly metabolized by CYP2D6 isoenzymes. CYP2D6 inhibitors, such as ritonavir, may impair metoprolol metabolism. Clinicians should be alert to exaggerated beta-blocker effects if metoprolol is given with these drugs. [5044] [5269]

Hydrochlorothiazide, HCTZ; Propranolol: (Moderate) Concurrent administration of propranolol with ritonavir may result in elevated propranolol plasma concentrations. Cardiac and neurologic events have been reported when ritonavir is concurrently administered with beta-blockers. Propranolol is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. Decreased beta-blocker dosage may be needed. [28315] [47165] [4998] [58664]

Hydrochlorothiazide, HCTZ; Valsartan: (Moderate) Concurrent use of lopinavir with valsartan may result in elevated valsartan serum concentrations. Valsartan is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. Monitor for increased toxicities if these drugs are given together. [56575] [61510] [61511] [61513] (Minor) Valsartan is a substrate of the hepatic efflux transporter MRP2 and ritonavir is an inhibitor of MRP2. Coadministration may increase systemic exposure to valsartan. Patients should be monitored for adverse effects of valsartan during coadministration. [28315] [29130] [36646] [39870] [60860]

Hydrocodone: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531]

Hydrocodone; Ibuprofen: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531]

Hydrocodone; Phenylephrine: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531]

Hydrocodone; Potassium Guaiacolsulfonate: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531]

Hydrocodone; Potassium Guaiacolsulfonate; Pseudoephedrine: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531]

Hydrocodone; Pseudoephedrine: (Moderate) Concomitant use of hydrocodone with ritonavir may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of ritonavir could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If ritonavir is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP3A4 and CYP2D6. Ritonavir is a strong inhibitor of CYP3A4 and also inhibits CYP2D6. [30379] [30391] [47165] [56303] [58531]

Hydroxychloroquine: (Major) Avoid coadministration of hydroxychloroquine and lopinavir due to the risk of additive QT prolongation. If use together is necessary, obtain an ECG at baseline to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Hydroxychloroquine prolongs the QT interval. Lopinavir is also associated with QT prolongation. [28341] [41806] [65157] [65170]

Hydroxyprogesterone: (Moderate) Concurrent administration of hydroxyprogesterone with ritonavir may result in elevated hydroxyprogesterone plasma concentrations. Hydroxyprogesterone is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [43316] [47165]

Hydroxyzine: (Major) Avoid coadministration of lopinavir with hydroxyzine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Postmarketing data indicate that hydroxyzine causes QT prolongation and torsade de pointes (TdP). [28341] [47129] [65157] [65170]

Ibrutinib: (Major) Avoid the concomitant use of ibrutinib and ritonavir; ibrutinib plasma concentrations may increase resulting in severe ibrutinib toxicity (e.g., hematologic toxicity, bleeding, infection). Ibrutinib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. When ibrutinib was administered with multiple doses of other strong CYP3A4 inhibitors, the C_{max} and AUC values of ibrutinib were increased significantly. [47165] [56410]

Ibuprofen; Oxycodone: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ritonavir is necessary. If ritonavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like ritonavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ritonavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. [39926] [47165]

Ibutilide: (Major) Avoid coadministration of lopinavir with ibutilide due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Ibutilide administration can cause QT prolongation and torsade de pointes (TdP); proarrhythmic events should be anticipated. [28341] [41830] [65157] [65170]

Idelalisib: (Severe) Concomitant use of idelalisib, a CYP3A4 substrate, and ritonavir, a strong CYP3A4 inhibitor, may increase the exposure of idelalisib. Additionally, idelalisib is a strong CYP3A inhibitor while ritonavir is a CYP3A substrate. The AUC of a sensitive CYP3A substrate was increased 5.4-fold when coadministered with idelalisib. Avoid concomitant use of idelalisib and ritonavir. [5070] [57675] (Major) Concomitant use of idelalisib, a CYP3A4 substrate, and lopinavir; ritonavir, a strong CYP3A4 inhibitor, may increase the exposure of idelalisib. Additionally, idelalisib is a strong CYP3A inhibitor while lopinavir and ritonavir are CYP3A substrates. The AUC of a sensitive CYP3A substrate was increased 5.4-fold when coadministered with idelalisib. Avoid concomitant use of idelalisib and lopinavir; ritonavir. [28341] [57675]

Ifosfamide: (Moderate) Monitor for a decrease in the efficacy of ifosfamide if coadministration with ritonavir is necessary. Ifosfamide is metabolized by CYP3A4 to its active alkylating metabolites. Ritonavir is a strong CYP3A4 inhibitor. Coadministration may decrease plasma concentrations of these active metabolites, decreasing the effectiveness of ifosfamide treatment. [47165] [51027]

Iloperidone: (Major) Avoid coadministration of lopinavir with iloperidone due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [28341] [36146] [65157] [65170] (Major) Reduce the iloperidone dose by one-half if coadministered with ritonavir. If ritonavir is

discontinued, increase the iloperidone dose to the previous level. Increased iloperidone exposure may occur with concurrent use. Iloperidone is a CYP3A4 substrate. Ritonavir is a strong CYP3A4 inhibitor. Coadministration of another strong CYP3A4 inhibitor increased the AUC of iloperidone and its metabolites P88 and P95 by 57%, 55% and 35%, respectively. [\[36146\]](#) [\[47165\]](#)

Imatinib: (Major) Protease Inhibitors inhibit cytochrome P450 CYP3A4 and may decrease the metabolism of imatinib and increase imatinib concentrations leading to an increased incidence of adverse reactions. In addition, because imatinib inhibits CYP2C9, CYP2D6, and CYP3A4/5, the metabolism of protease inhibitors may be decreased by imatinib. Close monitoring of the antiviral and antineoplastic responses is recommended. [\[28240\]](#) [\[28341\]](#)

Imipramine: (Moderate) A dose reduction of the tricyclic antidepressant (TCA) may be necessary when coadministered with ritonavir. Concurrent use may result in elevated TCA plasma concentrations. [\[47165\]](#)

Incretin Mimetics: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of protease inhibitors. Patients taking antidiabetic agents should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [\[30575\]](#) [\[50113\]](#) [\[50814\]](#)

Indacaterol: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [\[28318\]](#) [\[28341\]](#) [\[32901\]](#) [\[33925\]](#) [\[41231\]](#) [\[65157\]](#) [\[65170\]](#) (Moderate) Although no dosage adjustment of the 75 mcg indacaterol daily dose is needed, use caution if indacaterol and ritonavir are used concurrently. Monitor the patient clinically for beta-agonist side effects like tremor, nervousness, or fast, irregular heart rate. In addition, both ritonavir and long-acting beta agonists (LABAs) are associated with QT prolongation; concomitant use may increase the risk of QT prolongation. By inhibiting CYP3A4, CYP2D6, and P-glycoprotein, ritonavir reduces indacaterol metabolism. In drug interaction studies, coadministration of indacaterol 300 mcg (single dose) with ritonavir (300 mg twice daily for 7.5 days) resulted in a 1.7-fold increase in indacaterol exposure (AUC) whereas indacaterol maximal concentration (C_{max}) was unaffected. [\[44979\]](#) [\[47165\]](#) [\[51080\]](#) [\[59321\]](#) [\[60263\]](#)

Indacaterol; Glycopyrrolate: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [\[28318\]](#) [\[28341\]](#) [\[32901\]](#) [\[33925\]](#) [\[41231\]](#) [\[65157\]](#) [\[65170\]](#) (Moderate) Although no dosage adjustment of the 75 mcg indacaterol daily dose is needed, use caution if indacaterol and ritonavir are used concurrently. Monitor the patient clinically for beta-agonist side effects like tremor, nervousness, or fast, irregular heart rate. In addition, both ritonavir and long-acting beta agonists (LABAs) are associated with QT prolongation; concomitant use may increase the risk of QT prolongation. By inhibiting CYP3A4, CYP2D6, and P-glycoprotein, ritonavir reduces indacaterol metabolism. In drug interaction studies, coadministration of indacaterol 300 mcg (single dose) with ritonavir (300 mg twice daily for 7.5 days) resulted in a 1.7-fold increase in indacaterol exposure (AUC) whereas indacaterol maximal concentration (C_{max}) was unaffected. [\[44979\]](#) [\[47165\]](#) [\[51080\]](#) [\[59321\]](#) [\[60263\]](#)

Indinavir: (Minor) Coadministration with lopinavir; ritonavir increases plasma concentrations indinavir, due to the ritonavir component. When administered with standard doses of lopinavir; ritonavir (Kaletra), the indinavir dose should be decreased to 600 mg PO twice daily. Once daily lopinavir; ritonavir in combination with indinavir has not been studied. [\[28341\]](#) [\[46638\]](#) (Minor) Ritonavir inhibits the clearance of indinavir, and increased indinavir serum concentrations are seen with concurrent administration. In a pharmacokinetic study in healthy volunteers, the AUC of single indinavir dose increased 185 to 475% during concurrent ritonavir dosing; the mean indinavir half-life increased from 1.2 to 2.7 hours. In an observational study of HIV-infected patients, the combination of indinavir 1200 mg and ritonavir 100 mg, both twice daily, led to high systemic exposure to indinavir and was not well tolerated. The combination of indinavir 800 mg and ritonavir 100 mg twice daily resulted in therapeutic indinavir serum concentrations with improved tolerability and similar maximum serum concentrations as the approved indinavir dosage of 800 mg three times a day. Patients should be closely monitored for possible indinavir toxicity during concurrent administration; indinavir dosage reductions may be necessary. The recommended dosing regimen for this combination is indinavir 800 mg twice daily plus ritonavir 100 or 200 mg twice daily. [\[26120\]](#) [\[26121\]](#) [\[46638\]](#)

Inotuzumab Ozogamicin: (Major) Avoid coadministration of lopinavir with inotuzumab due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [\[28341\]](#) [\[62245\]](#) [\[65157\]](#) [\[65170\]](#)

Insulins: (Moderate) Monitor patients receiving insulin closely for changes in diabetic control, specifically hyperglycemia, when anti-retroviral protease inhibitors are instituted. New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. [\[30575\]](#) [\[60172\]](#)

Interferon Alfa-2b; Ribavirin: (Major) The concomitant use of ribavirin and anti-retroviral protease inhibitors should be done with caution as both can cause hepatic damage. Most protease inhibitors have been associated with episodes of liver toxicity, with lopinavir/low-dose ritonavir, fosamprenavir/low-dose ritonavir, and nelfinavir being less hepatotoxic and tipranavir/low-dose ritonavir being the most hepatotoxic. Hyperbilirubinemia is often associated with atazanavir and/or indinavir therapy but does not reflect liver damage and is related to the inhibition of UDP glucuronosyltransferase. Overall, the HCV-HIV International Panel recommends the management of hepatotoxicity should be based on the knowledge of the mechanisms involved for each drug. Furthermore, they state that there are lower

rates of liver-related mortality in coinfecting patients taking HAART, even in those with end-stage liver disease, compared with patients not receiving HAART. Closely monitor patients for treatment-associated toxicities, especially hepatic decompensation. [34878]

Interferons: (Moderate) The concomitant use of interferons and anti-retroviral protease inhibitors should be done with caution as both can cause hepatotoxicity. Closely monitor patients for treatment-associated toxicities, especially hepatic decompensation. Most protease inhibitors have been associated with episodes of liver toxicity. Cirrhotic chronic HCV infected patients co-infected with HIV receiving HAART and alpha interferons appear to be at increased risk for hepatic decompensation (e.g., Childs-Pugh score 6 or more) compared to patients not receiving HAART. The HCV-HIV International Panel recommends the management of hepatotoxicity should be based on the knowledge of the mechanisms involved for each drug. Furthermore, they state that there are lower rates of liver-related mortality in coinfecting patients taking HAART, even in those with end-stage liver disease, compared with patients not receiving HAART. [31649] [34878]

Irinotecan Liposomal: (Major) Avoid administration of ritonavir during treatment with irinotecan and for at least 1 week prior to starting therapy unless there are no therapeutic alternatives. Irinotecan is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Concomitant use may increase systemic exposure of irinotecan. [30469] [47165]

Irinotecan: (Major) Avoid administration of ritonavir during treatment with irinotecan and for at least 1 week prior to starting therapy unless there are no therapeutic alternatives. Irinotecan is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Concomitant use may increase systemic exposure of irinotecan. [30469] [47165]

Isavuconazonium: (Severe) Concomitant use of isavuconazonium with high-dose ritonavir (i.e., 400 mg every 12 hours) is contraindicated due to the risk for increased isavuconazole serum concentrations and serious adverse reactions, such as hepatic toxicity. Isavuconazole, the active moiety of isavuconazonium, is a sensitive substrate of hepatic isoenzyme CYP3A4; ritonavir is a strong inhibitor of this enzyme. According to the manufacturer, coadministration of isavuconazole with strong CYP3A4 inhibitors is contraindicated. Isavuconazole serum concentrations were increased 5-fold when coadministered with ketoconazole, another strong CYP3A4 inhibitor. Elevated ritonavir concentrations may also be seen with coadministration, as ritonavir is a substrate and isavuconazole is an inhibitor of CYP3A4 and the drug transporter P-glycoprotein (P-gp). [47165] [59042] (Major) Caution is advised when administering isavuconazonium concurrently with lopinavir; ritonavir. Coadministration may result in a loss of antiviral efficacy, due to decreased lopinavir; ritonavir plasma concentrations, as well as isavuconazole-related adverse effects, due to elevated isavuconazole plasma concentrations. Isavuconazole, the active moiety of isavuconazonium, is a substrate/inhibitor/inducer of the hepatic isoenzyme CYP3A4; lopinavir; ritonavir is a substrate and potent inhibitor of CYP3A4. During drug interaction studies in healthy adults, coadministration resulted in a 96% increase in isavuconazole serum concentrations and a 27% and 31% decrease in lopinavir and ritonavir concentrations, respectively. [28341] [59042]

Isoniazid, INH; Pyrazinamide, PZA; Rifampin: (Severe) Coadministration of rifampin and ritonavir results in markedly decreased ritonavir concentrations; HIV treatment failure and virologic resistance would be expected. Rifampin (300 or 600 mg daily for 10 days) decreases the AUC and C_{max} of ritonavir (500 mg every 12 hours for 20 days) by 35% and 25%, respectively. Coadministration may lead to loss of virologic response if ritonavir is the sole protease inhibitor and increase the risk of hepatotoxicity. The DHHS/NIH HIV Treatment Guidelines recommend ritonavir and rifampin should not be coadministered and suggest the consideration of alternative antimycobacterial agents, such as rifabutin. However, CDC guidelines suggest no change in ritonavir or rifampin dose when the drugs are coadministered, but this appears to only be in the setting of low-dose ritonavir (i.e., 100 mg or 200 mg twice daily) used to 'boost' concentrations of other protease inhibitors. In this setting it would be less likely to produce adverse events than higher ritonavir doses; however, a net CYP3A4 induction still results when used with rifampin. [1299] [30314] [46638] (Severe) The coadministration of lopinavir; ritonavir and rifampin is contraindicated. Concurrent use may lead to loss of virologic response and possible resistance to lopinavir; ritonavir, the class of protease inhibitors, or other antiretroviral agents. [28341] [30314] [46638]

Isoniazid, INH; Rifampin: (Severe) Coadministration of rifampin and ritonavir results in markedly decreased ritonavir concentrations; HIV treatment failure and virologic resistance would be expected. Rifampin (300 or 600 mg daily for 10 days) decreases the AUC and C_{max} of ritonavir (500 mg every 12 hours for 20 days) by 35% and 25%, respectively. Coadministration may lead to loss of virologic response if ritonavir is the sole protease inhibitor and increase the risk of hepatotoxicity. The DHHS/NIH HIV Treatment Guidelines recommend ritonavir and rifampin should not be coadministered and suggest the consideration of alternative antimycobacterial agents, such as rifabutin. However, CDC guidelines suggest no change in ritonavir or rifampin dose when the drugs are coadministered, but this appears to only be in the setting of low-dose ritonavir (i.e., 100 mg or 200 mg twice daily) used to 'boost' concentrations of other protease inhibitors. In this setting it would be less likely to produce adverse events than higher ritonavir doses; however, a net CYP3A4 induction still results when used with rifampin. [1299] [30314] [46638] (Severe) The coadministration of lopinavir; ritonavir and rifampin is contraindicated. Concurrent use may lead to loss of virologic response and possible resistance to lopinavir; ritonavir, the class of protease inhibitors, or other antiretroviral agents. [28341] [30314] [46638]

Isradipine: (Moderate) Concurrent administration of isradipine with protease inhibitors may result in elevated isradipine plasma concentrations and increased hypotensive effects. Isradipine is metabolized by the hepatic isoenzyme CYP3A4; protease inhibitors are potent inhibitors of this enzyme. In addition, ritonavir prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [29128] [32432] [47165]

Istradefylline: (Major) Do not exceed 20 mg once daily of istradefylline if administered with ritonavir as istradefylline exposure and adverse effects may increase. Ritonavir is a strong CYP3A4 inhibitor. Istradefylline exposure was increased by 2.5-fold when administered with a strong inhibitor in a drug interaction study. [47165] [64590]

Itraconazole: (Major) Avoid coadministration of lopinavir with itraconazole due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [28341] [40233] [57441] [65157] [65170] (Major) When administering itraconazole with ritonavir or ritonavir-containing drugs, do not exceed the maximum recommended itraconazole dose of 200 mg per day. Concurrent administration may result in increased exposure to both

drugs. Monitor patients for itraconazole and ritonavir-associated adverse effects. Both itraconazole and ritonavir are strong CYP3A4 inhibitors and substrates. [27983] [47165]

Ivabradine: (Severe) Coadministration of ivabradine and ritonavir is contraindicated. Ivabradine is primarily metabolized by CYP3A4; ritonavir is a strong CYP3A4 inhibitor. Coadministration will increase the plasma concentrations of ivabradine. Increased ivabradine concentrations may result in bradycardia exacerbation and conduction disturbances. [59430]

Ivacaftor: (Major) If ritonavir and ivacaftor are taken together, administer ivacaftor at the usual recommended dose but reduce the frequency to twice weekly. Ivacaftor is a CYP3A substrate and ritonavir is a CYP3A inhibitor. Coadministration with another strong CYP3A inhibitor increased ivacaftor exposure by 8.5-fold. [48524]

Ivosidenib: (Major) Avoid coadministration of ivosidenib with ritonavir due to increased plasma concentrations of ivosidenib, which increases the risk of QT prolongation. If concomitant use is unavoidable, reduce the dose of ivosidenib to 250 mg PO once daily. Monitor ECGs for QTc prolongation and monitor electrolytes, correcting any electrolyte abnormalities as clinically appropriate. If ritonavir is discontinued, wait at least 5 half-lives of ritonavir before increasing the dose of ivosidenib to the recommended dose of 500 mg PO once daily. Ivosidenib is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased ivosidenib single-dose AUC to 269% of control, with no change in Cmax. [47165] [63368] (Major) Avoid coadministration of lopinavir with ivosidenib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Interrupt or dose reduce ivosidenib if QT prolongation occurs. Prolongation of the QTc interval and ventricular arrhythmias have been reported in patients treated with ivosidenib. Lopinavir is associated with QT prolongation. [28341] [63368] [65157] [65170]

Ixabepilone: (Major) If possible, avoid coadministration of ixabepilone with ritonavir; concurrent use is expected to result in increased ixabepilone plasma concentrations and risk of adverse events. Consider alternative therapies before using ixabepilone with ritonavir. If coadministration of ixabepilone with ritonavir cannot be avoided, consider an ixabepilone dosage reduction to 20 mg/m² IV over 3 hours given every 3 weeks, as this dose is predicted to adjust the ixabepilone AUC to the range observed without inhibitors. Carefully monitor for adverse events. If a patient is already receiving ritonavir, a washout period of approximately 1 week is recommended before starting ixabepilone. Ixabepilone is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is a potent inhibitor of this enzyme. [10415] [47165]

Ketamine: (Moderate) Use caution if ritonavir is coadministered with ketamine due to the potential for increased ketamine exposure which may increase the risk of toxicity. Ketamine is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. [37294] [47165] [65210]

Ketoconazole: (Major) Avoid coadministration of lopinavir with ketoconazole due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [27982] [28341] [65157] [65170] (Major) When administering ketoconazole with ritonavir or ritonavir-containing drugs, do not exceed the maximum recommended ketoconazole dose of 200 mg per day. Concurrent administration of ritonavir (a potent CYP3A4 inhibitor) with ketoconazole (a CYP3A4 substrate) significantly increases ketoconazole systemic concentrations. In one drug interaction study, ketoconazole exposure was increased by 3.4-fold when given concurrently with ritonavir (500 mg twice daily). [27982] [47165]

Labetalol: (Moderate) Cardiac and neurologic events have been reported when ritonavir was concurrently administered with beta-blockers. [5044]

Lacosamide: (Moderate) Lacosamide causes PR interval prolongation in some patients. Caution is advised during coadministration of lacosamide with other drugs that cause PR prolongation, such as lopinavir; ritonavir, since further PR prolongation is possible. [28341] [34626] (Moderate) Use caution during concurrent use of lacosamide and ritonavir, particularly in patients with renal or hepatic impairment. Lacosamide is a CYP3A4 substrate; ritonavir is a potent inhibitor of CYP3A4. Patients with renal or hepatic impairment may have significantly increased exposure to lacosamide if coadministered with a strong CYP3A4 inhibitor. Dosage reduction of lacosamide may be necessary in this population. [28315] [34626]

Lamivudine, 3TC; Zidovudine, ZDV: (Minor) Since ritonavir induces glucuronidation, there is the potential for reduction in zidovudine, ZDV plasma concentrations during concurrent therapy with ritonavir. When coadministered with ritonavir, the AUC and Cmax of zidovudine, ZDV are decreased by 12% and 27%. The clinical significance of this interaction is unknown. [28315] [47165] [58664]

Lamivudine; Tenofovir Disoproxil Fumarate: (Moderate) Caution is advised when administering tenofovir, PMPA, a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate, concurrently with inhibitors of P-gp and BCRP, such as ritonavir. Coadministration may result in increased absorption of tenofovir. Monitor for tenofovir-associated adverse reactions. [28193] [58664] (Minor) There are varying results in reports of an interaction between tenofovir and lopinavir; ritonavir. In one report, the concurrent administration of tenofovir with lopinavir; ritonavir increased tenofovir Cmax 31%, AUC 34%, and Cmin 29%, with slight (15%) decreases in lopinavir Cmax and AUC; the alterations may be a food effect rather than a drug-drug interaction. In another report, lopinavir; ritonavir (400 mg; 100 mg PO twice daily for 14 days) increased the tenofovir (300 mg/day PO) Cmin 51% and AUC 32%, with no effect seen on lopinavir; ritonavir pharmacokinetics. While the clinical significance of this interaction is unknown, and is suspected to be insignificant, patients receiving lopinavir; ritonavir with tenofovir should be monitored for tenofovir-associated adverse events. [46638]

Lamotrigine: (Major) Adjustments in lamotrigine escalation and maintenance dose regimens are necessary with concomitant lopinavir; ritonavir use. Monitoring lamotrigine plasma concentrations may be indicated, particularly during dosage adjustments. Lamotrigine is metabolized predominantly by glucuronic acid conjugation, and lopinavir; ritonavir induces glucuronidation. During concurrent use of lamotrigine with lopinavir; ritonavir in 18 healthy subjects, induction of glucuronidation by lopinavir (400 mg twice daily); ritonavir (100 mg twice daily) decreased lamotrigine AUC, Cmax, and half-life by approximately 50% to 55.4%. [28451]

Lansoprazole: (Moderate) Increased exposure to lansoprazole may occur during concurrent administration of ritonavir. Although dosage adjustment of lansoprazole is not normally required, dosage reduction may be considered in patients receiving higher lansoprazole doses

(e.g., those with Zollinger-Ellison syndrome). Ritonavir is a strong CYP3A4 inhibitor. Lansoprazole is a CYP2C19 and CYP3A4 substrate. Coadministration of a dual CYP2C19/strong CYP3A4 inhibitor increased the lansoprazole AUC by an average of 4-times. [\[40596\]](#) [\[47165\]](#)

Lansoprazole; Naproxen: (Moderate) Increased exposure to lansoprazole may occur during concurrent administration of ritonavir. Although dosage adjustment of lansoprazole is not normally required, dosage reduction may be considered in patients receiving higher lansoprazole doses (e.g., those with Zollinger-Ellison syndrome). Ritonavir is a strong CYP3A4 inhibitor. Lansoprazole is a CYP2C19 and CYP3A4 substrate. Coadministration of a dual CYP2C19/strong CYP3A4 inhibitor increased the lansoprazole AUC by an average of 4-times. [\[40596\]](#) [\[47165\]](#)

Lanthanum Carbonate: (Major) Oral compounds known to interact with antacids, like protease inhibitors, should not be taken within 2 hours of dosing with lanthanum carbonate. If these agents are used concomitantly, space the dosing intervals appropriately. Monitor serum concentrations and clinical condition. [\[9126\]](#)

Lapatinib: (Major) Avoid coadministration of lapatinib with ritonavir due to increased plasma concentrations of lapatinib. If concomitant use is unavoidable, decrease the dose of lapatinib to 500 mg PO once daily. If ritonavir is discontinued, increase lapatinib to the indicated dose after a washout period of approximately 1 week. Lapatinib is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Concomitant use with another strong CYP3A4 inhibitor increased lapatinib exposure by 3.6-fold and increased the half-life of lapatinib by 1.7-fold. [\[33192\]](#) [\[47165\]](#) (Major) Avoid coadministration of lopinavir with lapatinib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Lapatinib has been associated with concentration-dependent QT prolongation; ventricular arrhythmias and torsade de pointes (TdP) have been reported in postmarketing experience. [\[28341\]](#) [\[33192\]](#) [\[65157\]](#) [\[65170\]](#)

Larotrectinib: (Major) Avoid coadministration of larotrectinib with ritonavir due to increased larotrectinib exposure resulting in increased treatment-related adverse effects. If coadministration cannot be avoided, reduce the larotrectinib dose by 50%. If ritonavir is discontinued, resume the original larotrectinib dose after 3 to 5 elimination half-lives of ritonavir. Larotrectinib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration of a strong CYP3A4 inhibitor increased the AUC of larotrectinib by 4.3-fold in a drug interaction study. [\[47165\]](#) [\[63780\]](#)

Ledipasvir; Sofosbuvir: (Moderate) Caution is warranted when ritonavir is administered with ledipasvir; sofosbuvir as there is a potential for elevated concentrations of ledipasvir and sofosbuvir. Ritonavir is an inhibitor of the transporter P-glycoprotein (P-gp). Both ledipasvir and sofosbuvir are substrates of P-gp. According to the manufacturer, no dosage adjustments are required when ledipasvir; sofosbuvir is administered concurrently with P-gp inhibitors; however, if these drugs are given together, consider increased monitoring for potential adverse effects. [\[28380\]](#) [\[47165\]](#) [\[58167\]](#)

Lefamulin: (Major) Avoid coadministration of lopinavir with lefamulin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Lefamulin has a concentration dependent QTc prolongation effect. The pharmacodynamic interaction potential to prolong the QT interval of the electrocardiogram between lefamulin and other drugs that effect cardiac conduction is unknown. [\[28341\]](#) [\[64576\]](#) [\[65157\]](#) [\[65170\]](#) (Major) Avoid coadministration of ritonavir with oral lefamulin due to increased lefamulin exposure; ritonavir may be administered with intravenous lefamulin. Lefamulin is a CYP3A4 and P-gp substrate and ritonavir is a P-gp and strong CYP3A4 inhibitor. Coadministration of a combined P-gp and strong CYP3A4 inhibitor increased the exposure of oral and intravenous lefamulin by 165% and 31%, respectively. [\[47165\]](#) [\[64576\]](#)

Lemborexant: (Major) Avoid coadministration of lemborexant and ritonavir as concurrent use is expected to significantly increase lemborexant exposure and the risk of adverse CNS effects. Lemborexant is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration of lemborexant with another strong CYP3A4 inhibitor increased the lemborexant AUC by up to 4.5-fold. [\[47165\]](#) [\[64870\]](#)

Lenvatinib: (Major) Avoid coadministration of lopinavir with lenvatinib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Prolongation of the QT interval has also been reported with lenvatinib therapy. [\[28341\]](#) [\[58782\]](#) [\[65157\]](#) [\[65170\]](#)

Lesinurad: (Moderate) Ritonavir may decrease the systemic exposure and therapeutic effect of lesinurad; monitor for potential reduction in efficacy. Ritonavir is a CYP2C9 inducer, and lesinurad is a CYP2C9 substrate. [\[26120\]](#) [\[28315\]](#) [\[60473\]](#)

Lesinurad; Allopurinol: (Moderate) Ritonavir may decrease the systemic exposure and therapeutic effect of lesinurad; monitor for potential reduction in efficacy. Ritonavir is a CYP2C9 inducer, and lesinurad is a CYP2C9 substrate. [\[26120\]](#) [\[28315\]](#) [\[60473\]](#)

Letermovir: (Moderate) A clinically relevant increase in the plasma concentration of ritonavir may occur if given with letermovir. In patients who are also receiving treatment with cyclosporine, the magnitude of this interaction may be amplified. Ritonavir is primarily metabolized by CYP3A. Letermovir is a moderate CYP3A4 inhibitor; however, when given with cyclosporine, the combined effect on CYP3A4 substrates may be similar to a strong CYP3A4 inhibitor. [\[47165\]](#) [\[62611\]](#) (Moderate) Administering lopinavir concurrently with letermovir may result in elevated concentrations of both drugs. The exposure to lopinavir may be further increased if the patient is receiving letermovir combined with cyclosporine. Closely monitor for adverse events, including fast or irregular heartbeats, severe rash, hepatotoxicity, and gastrointestinal events. Lopinavir is an inhibitor of the organic anion-transporting polypeptide (OATP1B1), and a substrate of CYP3A4. Letermovir is an OATP1B1 substrate and a moderate CYP3A4 inhibitor. When given with cyclosporine, the combined effect of letermovir and cyclosporine on CYP3A4 substrates may be similar to a strong CYP3A4 inhibitor. [\[28341\]](#) [\[56579\]](#) [\[61510\]](#) [\[61511\]](#) [\[61513\]](#) [\[62611\]](#)

Leuprolide: (Major) Avoid coadministration of lopinavir with leuprolide due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-

essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Androgen deprivation therapy (i.e., leuprolide) may prolong the QT/QTc interval. [28341] [43800] [65157] [65170]

Leuprolide; Norethindrone: (Major) Avoid coadministration of lopinavir with leuprolide due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Androgen deprivation therapy (i.e., leuprolide) may prolong the QT/QTc interval. [28341] [43800] [65157] [65170] (Moderate) Many anti-retroviral protease inhibitors may interact with hormonal agents like norethindrone, due to their actions on CYP metabolism, particularly CYP3A4. Data on the effects that protease inhibitors have on the serum concentrations of norethindrone are complex and are based mostly off of data with norethindrone-containing contraceptives. For example, ritonavir (also found in combinations like lopinavir; ritonavir, and used as a booster in many HIV treatment regimens) may decrease the metabolism of norethindrone, raising norethindrone concentrations. Women receiving norethindrone for hormone replacement or contraception should report potential hormonal adverse effects (e.g., bleeding pattern changes, acne, emotional lability) or any changes in efficacy (e.g., noted changes in bleeding patterns) to their prescribers. Because norethindrone-containing contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive norethindrone contraception concurrently with ritonavir should use an additional barrier method of contraception such as condoms. [58679] [7731]

Levalbuterol: (Major) Avoid coadministration of lopinavir with short-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28341] [33925] [65157] [65170]

Levobupivacaine: (Minor) Levobupivacaine is metabolized by CYP3A4 and CYP1A2. Known inhibitors of CYP3A4, such as ritonavir, may result in increased systemic levels of levobupivacaine when given concurrently, with potential for toxicity. Although not studied, dosage adjustments of levobupivacaine may be needed. [5637]

Levocetirizine: (Moderate) Coadministration of cetirizine and ritonavir resulted in a 42% increase in the AUC, 53% increase in half-life, and 29% decrease in clearance of cetirizine. Cetirizine did not alter ritonavir disposition. [28874] [33350]

Levofloxacin: (Major) Avoid coadministration of lopinavir with levofloxacin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Levofloxacin has been associated with a risk of QT prolongation and torsade de pointes (TdP). Although extremely rare, torsade de pointes has been reported during postmarketing surveillance of levofloxacin. [28341] [28421] [65157] [65170]

Levomethadyl: (Major) Agents that inhibit hepatic cytochrome P450 CYP 3A4, including ritonavir, may decrease the metabolism of levomethadyl, increase levomethadyl levels, and may precipitate severe arrhythmias including torsade de pointes. [4718]

Levomilnacipran: (Major) The adult dose of levomilnacipran should not exceed 80 mg/day during concurrent use of strong CYP3A4 inhibitors such as ritonavir. Levomilnacipran is partially metabolized by CYP3A4, and decreased metabolism of the drug can lead to an increased risk of adverse effects such as urinary retention. Additionally, ritonavir could further increase levomilnacipran concentrations by inhibiting its P-glycoprotein (P-gp) metabolism. [55469]

Levonorgestrel: (Major) Data on the effects that protease inhibitors have on the serum concentrations of estrogens and progestins are complex. Some protease inhibitors increase (i.e., ritonavir, lopinavir; ritonavir, nelfinavir, tipranavir) and others decrease (i.e., atazanavir, indinavir) the metabolism of hormonal contraceptives. The safety and efficacy of hormonal contraceptives may be affected if coadministered with protease inhibitors. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors concurrently should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with protease inhibitors to use an additional method of contraception to protect against unwanted pregnancy, unless other drug-specific recommendations are made by the manufacturer of the protease inhibitor. Furthermore, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with protease inhibitors should use an additional barrier method of contraception such as condoms. [46638] [5044]

Levorphanol: (Moderate) Ritonavir is an inhibitor of the cytochrome P450 3A4 isoenzyme and may decrease the metabolism of levorphanol if the two drugs are coadministered. [4718]

Lidocaine: (Moderate) Anti-retroviral protease inhibitors can inhibit hepatic cytochrome P450 3A4, an isoenzyme that is partially responsible for the metabolism of lidocaine. The concurrent use of systemic lidocaine and anti-retroviral protease inhibitors should be carefully monitored due to the potential for serious toxicity. [4718] [5172]

Linagliptin: (Moderate) Monitor for changes in glycemic control, specifically hyperglycemia, if ritonavir is administered concurrently with linagliptin. New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. [28315] [30575] [31240] [34557] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy, such as linagliptin, should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [28341] [30575]

Linagliptin; Metformin: (Moderate) Monitor for changes in glycemic control, specifically hyperglycemia, if ritonavir is administered concurrently with linagliptin. New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. [28315] [30575] [31240] [34557] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy, such as linagliptin, should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [28341] [30575] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Lisdexamfetamine: (Moderate) Warn patients that the risk of amphetamine toxicity may be increased during concurrent use of ritonavir, a strong CYP2D6 inhibitor. Amphetamines are partially metabolized by CYP2D6 and have serotonergic properties; inhibition of amphetamine metabolism may increase the risk of serotonin syndrome or other toxicity. If serotonin syndrome occurs, both the amphetamine and CYP2D6 inhibitor should be discontinued and appropriate medical treatment should be implemented. [25887] [29219] [33263] [47165] [57067]

Lithium: (Major) Avoid coadministration of lopinavir with lithium due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs are associated with QT prolongation. [28341] [59809] [59810] [59811] [65157] [65170]

Lofexidine: (Major) Avoid coadministration of lopinavir with lofexidine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [28341] [63161] [65157] [65170]

Lomitapide: (Severe) Concomitant use of ritonavir and lomitapide is contraindicated. If treatment with ritonavir is unavoidable, lomitapide should be stopped during the course of treatment. Ritonavir is a strong CYP3A4 inhibitor. The exposure to lomitapide was increased 27-fold in the presence of ketoconazole, a strong CYP3A4 inhibitor. [52698]

Long-acting beta-agonists: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28318] [28341] [32901] [33925] [41231] [65157] [65170]

Loperamide: (Major) Avoid coadministration of lopinavir with loperamide due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. At high doses, loperamide has been associated with serious cardiac toxicities, including syncope, ventricular tachycardia, QT prolongation, torsade de pointes (TdP), and cardiac arrest. [28341] [30106] [60864] [65157] [65170] (Moderate) Concurrent administration of loperamide and ritonavir may increase the risk for adverse reactions, such as CNS events and cardiac toxicities (i.e., syncope, ventricular tachycardia, QT prolongation, torsade de pointes, cardiac arrest). At high doses, loperamide has been associated with serious cardiac toxicities, including syncope, ventricular tachycardia, QT prolongation, TdP, and cardiac arrest. Loperamide is a substrate for the enzymes CYP3A4, CYP2D6, and the drug transporter P-glycoprotein (P-gp); ritonavir is an inhibitor of both enzymes and P-gp. When these drugs were administered together, an increase was seen in loperamide's C_{max} (17%), T_{max} (56%), AUC (223%), and amount excreted in the urine (118%). There was also a decrease in loperamide's oral clearance (70%). No CNS opioid effects (e.g., changes in pupil diameter, changes in pO₂ or pCO₂) were observed in this study, but it should be noted that because ritonavir is a potent P-gp inhibitor, it has the potential to hinder transport of loperamide out of the CNS and thereby depress respiratory ventilation. Monitor for depressed respiratory ventilation and adverse cardiac effects if these drugs are to be coadministered. [30106] [47165] [60864]

Loperamide; Simethicone: (Major) Avoid coadministration of lopinavir with loperamide due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. At high doses, loperamide has been associated with serious cardiac toxicities, including syncope, ventricular tachycardia, QT prolongation, torsade de pointes (TdP), and cardiac arrest. [28341] [30106] [60864] [65157] [65170] (Moderate) Concurrent administration of loperamide and ritonavir may increase the risk for adverse reactions, such as CNS events and cardiac toxicities (i.e., syncope, ventricular tachycardia, QT prolongation, torsade de pointes, cardiac arrest). At high doses, loperamide has been associated with serious cardiac toxicities, including syncope, ventricular tachycardia, QT prolongation, TdP, and cardiac arrest. Loperamide is a substrate for the enzymes CYP3A4, CYP2D6, and the drug transporter P-glycoprotein (P-gp); ritonavir is an inhibitor of both enzymes and P-gp. When these drugs were administered together, an increase was seen in loperamide's C_{max} (17%), T_{max} (56%), AUC (223%), and amount excreted in the urine (118%). There was also a decrease in loperamide's oral clearance (70%). No CNS opioid effects (e.g., changes in pupil diameter, changes in pO₂ or pCO₂) were observed in this study, but it should be noted that because ritonavir is a potent P-gp inhibitor, it has the potential to hinder transport of loperamide out of the CNS and thereby depress respiratory ventilation. Monitor for depressed respiratory ventilation and adverse cardiac effects if these drugs are to be coadministered. [30106] [47165] [60864]

Lorlatinib: (Major) Avoid coadministration of lorlatinib with lopinavir due to increased plasma concentrations of lorlatinib, which may increase the incidence and severity of adverse reactions of lorlatinib; plasma concentrations of lopinavir may also decrease. If concomitant use is unavoidable, decrease the starting dose of lorlatinib from 100 mg PO once daily to 75 mg PO once daily. In patients who have already had a dose reduction to 75 mg PO once daily due to adverse reactions, reduce the dose of lorlatinib to 50 mg PO once daily. If lopinavir; ritonavir is discontinued, increase the dose of lorlatinib after 3 plasma half-lives of lopinavir to the dose that was used before starting lopinavir; ritonavir. Lorlatinib is a CYP3A4 substrate and a moderate CYP3A4 inducer. Lopinavir; ritonavir is a CYP3A4 substrate and a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased the AUC and Cmax of lorlatinib by 42% and 24%, respectively. Concomitant administration of lopinavir with CYP3A4 inducers may decrease plasma concentrations, reducing efficacy and increasing the potential for viral resistance. [28341] [56579] [63732] (Major) Avoid coadministration of lorlatinib with ritonavir due to increased plasma concentrations of lorlatinib, which may increase the incidence and severity of adverse reactions of lorlatinib; plasma concentrations of ritonavir may also decrease. If concomitant use is unavoidable, decrease the starting dose of lorlatinib from 100 mg PO once daily to 75 mg PO once daily. In patients who have already had a dose reduction to 75 mg PO once daily due to adverse reactions, reduce the dose of lorlatinib to 50 mg PO once daily. If ritonavir is discontinued, increase the dose of lorlatinib after 3 plasma half-lives of ritonavir to the dose that was used before starting ritonavir. Lorlatinib is a CYP3A4 substrate and a moderate CYP3A4 inducer. Ritonavir is a CYP3A4 substrate and a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased the AUC and Cmax of lorlatinib by 42% and 24%, respectively. Concomitant administration of ritonavir with CYP3A4 inducers may decrease plasma concentrations, reducing efficacy and increasing the potential for viral resistance. [47165] [63732]

Losartan: (Moderate) Concurrent administration of losartan with ritonavir may result in elevated losartan plasma concentrations. Losartan is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [47165] [5339] [58664]

Lovastatin: (Severe) Concurrent use of lovastatin and anti-retroviral protease inhibitors is contraindicated. The risk of developing myopathy, rhabdomyolysis, and acute renal failure is substantially increased if lovastatin is administered concomitantly with anti-retroviral protease inhibitors. Lovastatin is a substrate of CYP3A4 and anti-retroviral protease inhibitors are strong inhibitors of CYP3A4; therefore, coadministration may result in substantial increases in plasma concentrations of lovastatin. [28604]

Lovastatin; Niacin: (Severe) Concurrent use of lovastatin and anti-retroviral protease inhibitors is contraindicated. The risk of developing myopathy, rhabdomyolysis, and acute renal failure is substantially increased if lovastatin is administered concomitantly with anti-retroviral protease inhibitors. Lovastatin is a substrate of CYP3A4 and anti-retroviral protease inhibitors are strong inhibitors of CYP3A4; therefore, coadministration may result in substantial increases in plasma concentrations of lovastatin. [28604]

Lumacaftor; Ivacaftor: (Major) If ritonavir and ivacaftor are taken together, administer ivacaftor at the usual recommended dose but reduce the frequency to twice weekly. Ivacaftor is a CYP3A substrate and ritonavir is a CYP3A inhibitor. Coadministration with another strong CYP3A inhibitor increased ivacaftor exposure by 8.5-fold. [48524] (Major) Lumacaftor; ivacaftor may decrease the therapeutic efficacy of lopinavir; ritonavir; avoid concurrent use if possible. If concomitant use of lopinavir; ritonavir is necessary, monitor antiretroviral efficacy and adjust therapy as necessary. Lumacaftor; ivacaftor dosage adjustment is not required when lopinavir; ritonavir is started in a patient already taking lumacaftor; ivacaftor. However, if lumacaftor; ivacaftor is initiated in a patient already taking lopinavir; ritonavir, reduce the dose of lumacaftor; ivacaftor to 1 tablet PO daily or 1 packet of oral granules every other day for the first week of treatment, and then increase to the usual recommended daily dose. This dosage adjustment is also necessary if lumacaftor; ivacaftor therapy has been interrupted for more than 1 week and re-initiated while the patient is taking lopinavir; ritonavir. The 1-week lead-in period at the lower lumacaftor; ivacaftor dosage allows for lumacaftor's induction of CYP3A to reach steady state. Lopinavir; ritonavir is a substrate and strong inhibitor of CYP3A. Ivacaftor is a CYP3A substrate, and lumacaftor is a strong CYP3A inducer. Lumacaftor's induction of CYP3A may decrease the systemic exposure of lopinavir; ritonavir and decrease its therapeutic efficacy. Although lopinavir; ritonavir is a strong CYP3A4 inhibitor, net ivacaftor exposure at steady state is not expected to exceed that achieved with ivacaftor monotherapy (i.e., 150 mg PO every 12 hours) because of lumacaftor's CYP3A induction. In pharmacokinetic studies, coadministration of lumacaftor; ivacaftor with another strong CYP3A4 inhibitor increased ivacaftor exposure by 4.3-fold. [28341] [56579] [59891] (Major) Lumacaftor; ivacaftor may decrease the therapeutic efficacy of ritonavir; avoid concurrent use if possible. If concomitant use of ritonavir is necessary, monitor antiretroviral efficacy and adjust therapy as necessary. Lumacaftor; ivacaftor dosage adjustment is not required when ritonavir is started in a patient already taking lumacaftor; ivacaftor. However, if lumacaftor; ivacaftor is initiated in a patient already taking ritonavir, reduce the dose of lumacaftor; ivacaftor to 1 tablet PO daily or 1 packet of oral granules every other day for the first week of treatment, and then increase to the usual recommended daily dose. This dosage adjustment is also necessary if lumacaftor; ivacaftor therapy has been interrupted for more than 1 week and re-initiated while the patient is taking ritonavir. The 1-week lead-in period at the lower lumacaftor; ivacaftor dosage allows for lumacaftor's induction of CYP3A to reach steady state. Ritonavir is a substrate and strong inhibitor of CYP3A. Ivacaftor is a CYP3A substrate, and lumacaftor is a strong CYP3A inducer. Lumacaftor's induction of CYP3A may decrease the systemic exposure of ritonavir and decrease its therapeutic efficacy. Although ritonavir is a strong CYP3A4 inhibitor, net ivacaftor exposure at steady state is not expected to exceed that achieved with ivacaftor monotherapy (i.e., 150 mg PO every 12 hours) because of lumacaftor's CYP3A induction. In pharmacokinetic studies, coadministration of lumacaftor; ivacaftor with another strong CYP3A4 inhibitor increased ivacaftor exposure by 4.3-fold. Lastly, ritonavir is also a substrate of the drug transporter P-glycoprotein (P-gp), and lumacaftor; ivacaftor has the potential to both induce and inhibit P-gp. The net effect on P-gp substrates is not clear, but their exposure may be affected. [28142] [59891]

Lumacaftor; Ivacaftor: (Major) Lumacaftor; ivacaftor may decrease the therapeutic efficacy of lopinavir; ritonavir; avoid concurrent use if possible. If concomitant use of lopinavir; ritonavir is necessary, monitor antiretroviral efficacy and adjust therapy as necessary. Lumacaftor; ivacaftor dosage adjustment is not required when lopinavir; ritonavir is started in a patient already taking lumacaftor; ivacaftor. However, if lumacaftor; ivacaftor is initiated in a patient already taking lopinavir; ritonavir, reduce the dose of lumacaftor; ivacaftor to 1 tablet PO daily or 1 packet of oral granules every other day for the first week of treatment, and then increase to the usual recommended daily dose. This dosage adjustment is also necessary if lumacaftor; ivacaftor therapy has been interrupted for more than 1 week and re-initiated while the patient is taking lopinavir; ritonavir. The 1-week lead-in period at the lower lumacaftor; ivacaftor dosage allows for lumacaftor's induction of CYP3A to reach steady state. Lopinavir; ritonavir is a substrate and strong inhibitor of CYP3A. Ivacaftor is a CYP3A substrate, and lumacaftor is a strong CYP3A inducer. Lumacaftor's induction of CYP3A may decrease the systemic exposure of lopinavir; ritonavir and decrease its therapeutic efficacy. Although lopinavir; ritonavir is a strong CYP3A4 inhibitor, net ivacaftor exposure at steady state is not expected to exceed that achieved with ivacaftor monotherapy (i.e., 150 mg PO every 12 hours)

because of lumacaftor's CYP3A induction. In pharmacokinetic studies, coadministration of lumacaftor; ivacaftor with another strong CYP3A4 inhibitor increased ivacaftor exposure by 4.3-fold. [28341] [56579] [59891] (Major) Lumacaftor; ivacaftor may decrease the therapeutic efficacy of ritonavir; avoid concurrent use if possible. If concomitant use of ritonavir is necessary, monitor antiretroviral efficacy and adjust therapy as necessary. Lumacaftor; ivacaftor dosage adjustment is not required when ritonavir is started in a patient already taking lumacaftor; ivacaftor. However, if lumacaftor; ivacaftor is initiated in a patient already taking ritonavir, reduce the dose of lumacaftor; ivacaftor to 1 tablet PO daily or 1 packet of oral granules every other day for the first week of treatment, and then increase to the usual recommended daily dose. This dosage adjustment is also necessary if lumacaftor; ivacaftor therapy has been interrupted for more than 1 week and re-initiated while the patient is taking ritonavir. The 1-week lead-in period at the lower lumacaftor; ivacaftor dosage allows for lumacaftor's induction of CYP3A to reach steady state. Ritonavir is a substrate and strong inhibitor of CYP3A. Ivacaftor is a CYP3A substrate, and lumacaftor is a strong CYP3A inducer. Lumacaftor's induction of CYP3A may decrease the systemic exposure of ritonavir and decrease its therapeutic efficacy. Although ritonavir is a strong CYP3A4 inhibitor, net ivacaftor exposure at steady state is not expected to exceed that achieved with ivacaftor monotherapy (i.e., 150 mg PO every 12 hours) because of lumacaftor's CYP3A induction. In pharmacokinetic studies, coadministration of lumacaftor; ivacaftor with another strong CYP3A4 inhibitor increased ivacaftor exposure by 4.3-fold. Lastly, ritonavir is also a substrate of the drug transporter P-glycoprotein (P-gp), and lumacaftor; ivacaftor has the potential to both induce and inhibit P-gp. The net effect on P-gp substrates is not clear, but their exposure may be affected. [28142] [59891]

Lumateperone: (Major) Avoid coadministration of lumateperone and ritonavir as concurrent use may increase lumateperone exposure and the risk of adverse effects. Lumateperone is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased lumateperone exposure by approximately 4-fold. [47165] [64885]

Lurasidone: (Severe) Concurrent use of lurasidone with strong CYP3A4 inhibitors, such as ritonavir, is contraindicated. Lurasidone is primarily metabolized by CYP3A4. Increased lurasidone plasma concentrations are expected when the drug is co-administered with inhibitors of CYP3A4. [28315] [42227] [47165]

Macimorelin: (Major) Avoid coadministration of lopinavir with macimorelin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Sufficient washout time of drugs that are known to prolong the QT interval prior to administration of macimorelin is recommended. Treatment with macimorelin has been associated with an increase in the corrected QT (QTc) interval. Lopinavir is associated with QT prolongation. [28341] [62723] [65157] [65170]

Macitentan: (Major) Avoid concurrent use of macitentan and ritonavir. Ritonavir is a strong inhibitor of CYP3A4. Coadministration of macitentan with another strong CYP3A4 inhibitor approximately doubled macitentan exposure. Consider alternative treatment options for pulmonary hypertension if treatment with ritonavir is necessary. [56260]

Maprotiline: (Major) Avoid coadministration of lopinavir with maprotiline due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Maprotiline has been reported to prolong the QT interval, particularly in overdose or with higher-dose prescription therapy (elevated serum concentrations). Cases of long QT syndrome and torsade de pointes (TdP) tachycardia have been described with maprotiline use, but rarely occur when the drug is used alone in normal prescribed doses and in the absence of other known risk factors for QT prolongation. Limited data are available regarding the safety of maprotiline in combination with other QT-prolonging drugs. [28341] [28415] [4951] [5491] [65157] [65170] (Moderate) Ritonavir potently inhibits the CYP2D6 and CYP3A4 isozymes, and thus may inhibit the metabolism of maprotiline. Since the magnitude of the interaction with the maprotiline is difficult to predict but may be significant, monitor patients receiving ritonavir and maprotiline concurrently closely. Adjust the dosage of maprotiline based on therapeutic response. Maprotiline serum concentration monitoring may be useful to guide adjustments and prevent toxicity. [28759] [46638] [47165] [5542]

Maraviroc: (Major) Coadministration of maraviroc (a substrate of CYP3A, P-gp, and OATP1B1) with lopinavir; ritonavir (a strong CYP3A4 inhibitor and P-gp/OATP1B1 inhibitor) has been reported to increase the maraviroc AUC by 4-fold. Reduce the dose of maraviroc when coadministered with strong CYP3A inhibitors; coadministration of maraviroc with strong CYP3A inhibitors is contraindicated in patients with CrCl less than 30 mL/min. Adjust the maraviroc dosage as follows when administered with lopinavir; ritonavir (with or without a concomitant CYP3A inducer): adults and children weighing 40 kg or more: 150 mg PO twice daily; children weighing 30 to 39 kg: 100 mg PO twice daily; children weighing 20 to 29 kg: 75 mg PO twice daily (or 80 mg PO twice daily for solution); children weighing 10 to 19 kg: 50 mg PO twice daily. [28341] [28380] [33473] [46638] [56579] [61510] (Major) Coadministration of maraviroc (a substrate of CYP3A, P-gp, MRP2) with ritonavir (a strong CYP3A4 inhibitor and P-gp/MRP2 inhibitor) has been reported to significantly increase maraviroc concentrations. Reduce the dose of maraviroc when coadministered with strong CYP3A inhibitors; coadministration of maraviroc with strong CYP3A inhibitors is contraindicated in patients with CrCl less than 30 mL/min. Adjust the maraviroc dosage as follows when administered with ritonavir (with or without a concomitant CYP3A inducer): adults and children weighing 40 kg or more: 150 mg PO twice daily; children weighing 30 to 39 kg: 100 mg PO twice daily; children weighing 20 to 29 kg: 75 mg PO twice daily (or 80 mg PO twice daily for solution); children weighing 10 to 19 kg: 50 mg PO twice daily. [28380] [33473] [46638] [60845]

Meclizine: (Moderate) Concurrent administration of meclizine with ritonavir may result in elevated meclizine plasma concentrations. Meclizine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [43856] [47165] [58664]

Medroxyprogesterone: (Major) Coadministration of medroxyprogesterone, a CYP3A substrate with ritonavir, a strong CYP3A inhibitor should be avoided since it is expected to increase concentrations of medroxyprogesterone acetate. Formal drug interaction studies have not been conducted; however, medroxyprogesterone is metabolized primarily by hydroxylation via the CYP3A4 in vitro. [28380] [34557] [47165] [57648]

Mefloquine: (Major) Avoid coadministration of lopinavir with mefloquine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. There is evidence that the use of halofantrine after mefloquine causes a significant lengthening of the QTc interval. Mefloquine alone has not been

reported to cause QT prolongation. [28301] [28341] [65157] [65170] (Moderate) The plasma concentrations of mefloquine may be elevated when administered concurrently with ritonavir. Clinical monitoring for adverse effects, such as GI or neuropsychiatric effects, is recommended during coadministration. Ritonavir is a strong inhibitor of CYP3A4 and P-glycoprotein (P-gp) inhibitor, while mefloquine is a CYP3A4 and P-gp substrate. [28301] [47165]

Meloxicam: (Moderate) Concurrent administration of meloxicam with ritonavir may result in elevated meloxicam plasma concentrations. Meloxicam is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [47165] [58664] [6352]

Meperidine: (Severe) Concomitant use of high-dose, long-term meperidine therapy with ritonavir is not recommended due to the increased concentration of the neurotoxic metabolite of meperidine, normeperidine. Ritonavir is associated with a 62% decrease in meperidine AUC thought to be due to increased meperidine metabolism. The AUC and Cmax of normeperidine, the toxic metabolite of meperidine, increased 47% and 87%, respectively, with concurrent administration of ritonavir. [28315] [46638] [47165] [58664]

Meperidine; Promethazine: (Severe) Concomitant use of high-dose, long-term meperidine therapy with ritonavir is not recommended due to the increased concentration of the neurotoxic metabolite of meperidine, normeperidine. Ritonavir is associated with a 62% decrease in meperidine AUC thought to be due to increased meperidine metabolism. The AUC and Cmax of normeperidine, the toxic metabolite of meperidine, increased 47% and 87%, respectively, with concurrent administration of ritonavir. [28315] [46638] [47165] [58664] (Major) Avoid coadministration of lopinavir with promethazine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Promethazine, a phenothiazine, is also associated with a possible risk for QT prolongation. [28225] [28341] [55578] [65157] [65170]

Mephobarbital: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [28341] [46638] (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [46638]

Mesoridazine: (Major) QT prolongation in patients taking lopinavir; ritonavir has been reported. Coadministration of lopinavir; ritonavir with other drugs that prolong the QT interval, such as mesoridazine, may result in additive QT prolongation. [28341] [4951] [5831]

Mestranol; Norethindrone: (Major) Ritonavir increases the metabolism of mestranol. Women receiving hormonal contraceptives and ritonavir should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with ritonavir to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with ritonavir should use an additional barrier method of contraception such as condoms. [5044] [7731] (Moderate) Many anti-retroviral protease inhibitors may interact with hormonal agents like norethindrone, due to their actions on CYP metabolism, particularly CYP3A4. Data on the effects that protease inhibitors have on the serum concentrations of norethindrone are complex and are based mostly off of data with norethindrone-containing contraceptives. For example, ritonavir (also found in combinations like lopinavir; ritonavir, and used as a booster in many HIV treatment regimens) may decrease the metabolism of norethindrone, raising norethindrone concentrations. Women receiving norethindrone for hormone replacement or contraception should report potential hormonal adverse effects (e.g., bleeding pattern changes, acne, emotional lability) or any changes in efficacy (e.g., noted changes in bleeding patterns) to their prescribers. Because norethindrone-containing contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive norethindrone contraception concurrently with ritonavir should use an additional barrier method of contraception such as condoms. [58679] [7731]

Metaproterenol: (Major) Avoid coadministration of lopinavir with short-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28341] [33925] [65157] [65170]

Metformin: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Metformin; Pioglitazone: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Metformin; Repaglinide: (Moderate) Coadministration of repaglinide and protease inhibitors may increase or decrease glucose concentrations and increase repaglinide AUC; if coadministration is necessary, repaglinide dosage adjustment may be necessary and increased frequency of glucose monitoring are recommended. New onset diabetes mellitus, exacerbation of diabetes mellitus, and

hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. In addition, repaglinide is a substrate of the hepatic isoenzyme CYP3A4 and the drug transporter organic anion transporting polypeptide OATP1B1; protease inhibitors are potent CYP3A4 inhibitors and inhibitors of OATP. [29751] [31281] [36049] [61511] [61513] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Metformin; Rosiglitazone: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Metformin; Saxagliptin: (Major) The metabolism of saxagliptin is primarily mediated by CYP3A4/5. The saxagliptin dose is limited to 2.5 mg once daily when coadministered with a strong CYP 3A4/5 inhibitor such as the ritonavir component of lopinavir; ritonavir. In addition, new onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [28341] [30575] [36111] (Major) The metabolism of saxagliptin is primarily mediated by CYP3A4/5. The saxagliptin dose is limited to 2.5 mg once daily when coadministered with a strong CYP3A4/5 inhibitor such as ritonavir. New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have also been reported with use of anti-retroviral protease inhibitors, such as ritonavir. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [36111] [7238] [7335] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Metformin; Sitagliptin: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic agents should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30575] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30480] [30575]

Methadone: (Major) Avoid coadministration of lopinavir with methadone due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Methadone is associated with an increased risk for QT prolongation and torsade de pointes (TdP), especially at higher doses (more than 200 mg/day but averaging approximately 400 mg/day in adult patients). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. [28319] [28320] [28321] [28322] [28341] [33136] [65157] [65170] (Moderate) Coadministration of ritonavir with methadone has resulted in decreased methadone plasma concentrations. However, because methadone is metabolized by multiple CYP450 enzymes, including CYP3A4, CYP2C19, CYP2C9, and CYP2D6, and ritonavir is known to inhibit CYP3A4 and CYP2D6 and induce CYP2C19 and CYP2C9, the potential for increased methadone exposure should also be considered with concomitant administration. Therefore, concurrent use may increase or prolong opioid effects, resulting in fatal overdose or may decrease methadone efficacy or produce onset of withdrawal symptoms in patients physically dependent on methadone. Monitor for respiratory depression, sedation, and signs of opioid withdrawal. Consider adjusting the methadone dose until stable drug effects are achieved. If ritonavir is discontinued, and its CYP450 effects decline, methadone plasma concentrations may increase or decrease. Closely monitor for increased opioid adverse effects and for evidence of withdrawal and adjust the methadone dose as necessary when ritonavir is discontinued. [33136] [47165]

Methamphetamine: (Moderate) Warn patients that the risk of amphetamine toxicity may be increased during concurrent use of ritonavir, a strong CYP2D6 inhibitor. Amphetamines are partially metabolized by CYP2D6 and have serotonergic properties; inhibition of amphetamine metabolism may increase the risk of serotonin syndrome or other toxicity. If serotonin syndrome occurs, both the amphetamine and CYP2D6 inhibitor should be discontinued and appropriate medical treatment should be implemented. [25887] [29219] [33263] [47165] [57067]

Methohexital: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [28341] [46638] (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased

doses of anticonvulsants may be required due to metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [\[46638\]](#)

Methylergonovine: (Severe) Coadministration of ergot alkaloids with potent inhibitors of CYP3A4, like anti-retroviral protease inhibitors is considered contraindicated due to the risk of acute ergot toxicity (e.g., vasospasm leading to cerebral ischemia, peripheral ischemia and/or other serious effects). Several case reports have established the clinical significance of this interaction in the medical literature. In some cases, fatal interactions have occurred. [\[28142\]](#) [\[28341\]](#) [\[28731\]](#) [\[28839\]](#) [\[28995\]](#) [\[32432\]](#) [\[46638\]](#) [\[5018\]](#) [\[5044\]](#) [\[5623\]](#) [\[5747\]](#) [\[8102\]](#)

Methylprednisolone: (Moderate) Coadministration of methylprednisolone with ritonavir may cause elevated methylprednisolone serum concentrations, potentially resulting in Cushing's syndrome and adrenal suppression. Monitor closely. For long-term use, consider an alternative corticosteroid, such as beclomethasone and prednisolone, if appropriate, whose concentrations are less affected by strong CYP3A4 inhibitors. Methylprednisolone is a CYP3A4 substrate and ritonavir is a strong inhibitor of CYP3A4. [\[30015\]](#) [\[47165\]](#) [\[58664\]](#)

Methysergide: (Severe) Coadministration of ergot alkaloids with potent inhibitors of CYP3A4, like anti-retroviral protease inhibitors is considered contraindicated due to the risk of acute ergot toxicity (e.g., vasospasm leading to cerebral ischemia, peripheral ischemia and/or other serious effects). Several case reports have established the clinical significance of this interaction in the medical literature. In some cases, fatal interactions have occurred. [\[28142\]](#) [\[28341\]](#) [\[28731\]](#) [\[28839\]](#) [\[28995\]](#) [\[32432\]](#) [\[46638\]](#) [\[5018\]](#) [\[5044\]](#) [\[5623\]](#) [\[5747\]](#) [\[8102\]](#)

Metoclopramide: (Moderate) Concurrent administration of metoclopramide with ritonavir may result in elevated plasma concentrations of metoclopramide. Metoclopramide is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[34515\]](#) [\[47165\]](#) [\[58664\]](#)

Metoprolol: (Moderate) Metoprolol is significantly metabolized by CYP2D6 isoenzymes. CYP2D6 inhibitors, such as ritonavir, may impair metoprolol metabolism. Clinicians should be alert to exaggerated beta-blocker effects if metoprolol is given with these drugs. [\[5044\]](#) [\[5269\]](#)

Metronidazole: (Major) Avoid coadministration of lopinavir with metronidazole due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Potential QT prolongation has been reported in limited case reports with metronidazole. Additionally, oral solutions of lopinavir; ritonavir contain ethanol which can produce disulfiram-like reactions when coadministered with metronidazole. [\[28341\]](#) [\[57377\]](#) [\[57378\]](#) [\[65157\]](#) [\[65170\]](#) (Major) Medications with significant alcohol content should not be ingested during therapy with metronidazole and should be avoided for 3 days after therapy is discontinued. Oral solutions of ritonavir contain ethanol. Administration of ritonavir oral solution to patients receiving or who have recently received disulfiram or metronidazole may result in disulfiram-like reactions. A disulfiram reaction would not be expected to occur with non-ethanol containing formulations of ritonavir. [\[28315\]](#) [\[28581\]](#) [\[47165\]](#)

Mexiletine: (Major) Ritonavir is an inhibitor of CYP3A4 and CYP2D6 (in vitro), and may increase exposure to drugs metabolized by these enzymes, such as mexiletine. Increased mexiletine serum concentrations may increase the risk for adverse reactions. [\[47165\]](#) [\[60002\]](#)

Midazolam: (Major) The use of oral midazolam and anti-retroviral protease inhibitors is contraindicated due to the potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression. Parenteral midazolam can be used with protease inhibitors in a setting that allows for close clinical monitoring with the ability to manage respiratory depression or sedation should they occur; a reduction in the dose of parenteral midazolam may be warranted. Lorazepam, oxazepam, or temazepam may be safer alternatives, as these benzodiazepines are not oxidatively metabolized. Midazolam is metabolized by hepatic isozyme CYP3A4. Protease inhibitors have been shown to increase oral midazolam AUCs by up to 3-fold, resulting in clinically significant potentiation of sedation. [\[28142\]](#) [\[28341\]](#) [\[28731\]](#) [\[28839\]](#) [\[28995\]](#) [\[29012\]](#) [\[31320\]](#) [\[32432\]](#) [\[44859\]](#) [\[47165\]](#)

Midostaurin: (Major) Avoid coadministration of lopinavir with midostaurin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [\[28341\]](#) [\[61906\]](#) [\[65157\]](#) [\[65170\]](#) (Major) Avoid the concomitant use of midostaurin and ritonavir as significantly increased exposure of midostaurin and its active metabolites may occur resulting in increased toxicity. Consider an alternative agent to replace ritonavir. If coadministration cannot be avoided, monitor patients for signs and symptoms of midostaurin toxicity (e.g., gastrointestinal toxicity, hematologic toxicity, bleeding, and infection), particularly during the first week of midostaurin therapy for systemic mastocytosis/mast cell leukemia and the first week of each cycle of midostaurin therapy for acute myeloid leukemia. Midostaurin is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. The AUC values of midostaurin and its metabolites CGP62221 and CGP52421 increased by 10.4-fold, 3.5-fold, and 1.2-fold, respectively, when midostaurin was administered with another strong CYP3A4 inhibitor in a drug interaction study. The C_{min} (trough) levels of midostaurin and its metabolites CGP62221 and CGP52421 on day 28 increased by 2.1-fold, 1.2-fold, and 1.3-fold, respectively, when midostaurin was administered with another strong CYP3A4 inhibitor compared with day 21 C_{min} levels with midostaurin alone in another drug interaction study. [\[47165\]](#) [\[61906\]](#)

Mifepristone: (Major) Avoid coadministration of lopinavir with mifepristone due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Monitor patients for lopinavir-related adverse effects (e.g., diarrhea, nausea, vomiting, fast irregular heartbeat, hypokalemia, pancreatic or hepatic dysfunction). Mifepristone is a strong CYP3A4 inhibitor and may lead to an increase in serum concentrations of lopinavir, a CYP3A4 substrate. Mifepristone is also associated with dose-related prolongation of the QT interval. Lopinavir is associated with QT prolongation. [\[28003\]](#) [\[28341\]](#) [\[48697\]](#) [\[65157\]](#) [\[65170\]](#) (Major) Avoid coadministration of ritonavir with mifepristone if possible because increased serum concentrations of either drug may result. The benefit of concomitant use of these agents should be carefully weighed against the potential risks. The CYP3A4 metabolism of mifepristone may be inhibited by ritonavir, a strong CYP3A4 inhibitor. In addition, mifepristone is a strong CYP3A4 inhibitor and may lead to an increase in serum concentrations of CYP3A4 substrates, such as ritonavir. When mifepristone is used in the treatment of Cushing's syndrome, coadministration with strong CYP3A inhibitors should be done only when necessary, and in such cases, the dose of mifepristone should be limited to 600 mg per day. In a patient already receiving ritonavir, initiate mifepristone at a dose of 300 mg and titrate to a maximum of 600 mg if clinically indicated. If therapy with ritonavir is initiated in a patient already receiving mifepristone 300

mg, mifepristone dosage adjustments are not required. If therapy with ritonavir is initiated in a patient already receiving mifepristone 600 mg, reduce dose of mifepristone to 300 mg and titrate to a maximum of 600 mg if clinically indicated. If therapy with ritonavir is initiated in a patient already receiving mifepristone 900 mg or 1,200 mg, reduce the mifepristone dose to 600 mg. [\[28003\]](#) [\[47165\]](#) [\[48697\]](#)

Miglitol: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. [\[7238\]](#) [\[7335\]](#)

Mirabegron: (Moderate) Concurrent administration of mirabegron with ritonavir may result in elevated plasma concentrations of ritonavir. Mirabegron is a moderate inhibitor of CYP2D6. Ritonavir is a CYP2D6 substrate. Caution and close monitoring are advised if these drugs are administered together. [\[28380\]](#) [\[47165\]](#) [\[51111\]](#)

Mirtazapine: (Major) Avoid coadministration of lopinavir with mirtazapine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Mirtazapine has been associated with dose-dependent prolongation of the QT interval. Torsade de pointes (TdP) has been reported postmarketing, primarily in overdose or in patients with other risk factors for QT prolongation. [\[28341\]](#) [\[40942\]](#) [\[65157\]](#) [\[65170\]](#) (Moderate) The plasma concentrations of mirtazapine may be elevated when administered concurrently with ritonavir. Clinical monitoring for adverse effects, such as CNS or GI effects, is recommended during coadministration. Ritonavir is a strong CYP3A4 inhibitor, while mirtazapine is a CYP3A4. Coadministration with another strong CYP3A4 inhibitor increased mirtazapine exposure by approximately 50%. [\[40942\]](#) [\[47165\]](#)

Mitomycin: (Moderate) The plasma concentrations of mitomycin may be elevated when administered concurrently with ritonavir. Clinical monitoring for adverse effects, such as myelosuppression and pulmonary toxicity, is recommended during coadministration. Ritonavir is a P-glycoprotein (P-gp) inhibitor, while mitomycin is a P-gp substrate. [\[28380\]](#) [\[34516\]](#) [\[56579\]](#)

Mitotane: (Severe) Coadministration of lopinavir; ritonavir and mitotane is contraindicated due to the potential for reduced antiretroviral efficacy and the potential development of viral resistance. If coadministration cannot be avoided, monitor for decreased efficacy of lopinavir; ritonavir. Mitotane is a strong CYP3A4 inducer and both lopinavir and ritonavir are CYP3A4 substrates; coadministration may result in decreased plasma concentrations of lopinavir; ritonavir. Another strong CYP3A inducer, rifampin (300 or 600 mg daily for 10 days), decreased the AUC and Cmax of ritonavir (500 mg every 12 hours for 20 days) by 35% and 25%, respectively. [\[28341\]](#) [\[41934\]](#) [\[46638\]](#) [\[56579\]](#) (Major) Avoid the concomitant use of mitotane with ritonavir due to the potential for reduced antiretroviral efficacy and the potential development of viral resistance. If coadministration cannot be avoided, monitor for decreased efficacy of ritonavir. Mitotane is a strong CYP3A4 inducer and ritonavir is a CYP3A4 substrate; coadministration may result in decreased plasma concentrations of ritonavir. Another strong CYP3A inducer, rifampin (300 or 600 mg daily for 10 days), decreased the AUC and Cmax of ritonavir (500 mg every 12 hours for 20 days) by 35% and 25%, respectively. [\[41934\]](#) [\[46638\]](#)

Modafinil: (Major) Concurrent administration of modafinil with ritonavir may result in elevated plasma concentrations of modafinil and decreased concentrations of ritonavir. Modafinil is a substrate and inducer of the hepatic isoenzyme CYP3A4; ritonavir is a CYP3A4 substrate. In addition, ritonavir is a potent CYP3A4 inhibitor. Because the resultant effect of coadministration of a CYP3A4 inducer (modafinil) and inhibitor (ritonavir) on the plasma concentrations of these drugs is not defined, caution and close monitoring are advised if these drugs are administered together. [\[41243\]](#) [\[58664\]](#)

Mometasone: (Moderate) Coadministration of mometasone with ritonavir (a strong CYP3A4 inhibitor) may cause mometasone serum concentrations to increase, potentially resulting in Cushing's syndrome and adrenal suppression. Consider use of an alternative corticosteroid whose concentrations are less affected by strong CYP3A4 inhibitors, such as beclomethasone and prednisolone, especially during long-term treatment. [\[28341\]](#) [\[47165\]](#) [\[58620\]](#)

Morphine: (Moderate) Close clinical monitoring is advised when administering morphine with ritonavir due to an increased potential for morphine-related adverse events, including hypotension, respiratory depression, profound sedation, coma, and death. Dosage reductions of morphine and/or ritonavir may be required. Morphine is a substrate of the drug efflux transporter P-glycoprotein (P-gp); ritonavir is an inhibitor of this efflux protein. Coadministration may cause an approximate 2-fold increase in morphine exposure. [\[28380\]](#) [\[34557\]](#) [\[40951\]](#)

Morphine; Naltrexone: (Moderate) Close clinical monitoring is advised when administering morphine with ritonavir due to an increased potential for morphine-related adverse events, including hypotension, respiratory depression, profound sedation, coma, and death. Dosage reductions of morphine and/or ritonavir may be required. Morphine is a substrate of the drug efflux transporter P-glycoprotein (P-gp); ritonavir is an inhibitor of this efflux protein. Coadministration may cause an approximate 2-fold increase in morphine exposure. [\[28380\]](#) [\[34557\]](#) [\[40951\]](#)

Moxifloxacin: (Major) Avoid coadministration of lopinavir with moxifloxacin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Quinolones have been associated with a risk of QT prolongation. Although extremely rare, torsade de pointes (TdP) has been reported during postmarketing surveillance of moxifloxacin. These reports generally involved patients with concurrent medical conditions or concomitant medications that may have been contributory. [\[28341\]](#) [\[28423\]](#) [\[5149\]](#) [\[5150\]](#) [\[65157\]](#) [\[65170\]](#) (Moderate) Concomitant use of ritonavir with moxifloxacin may increase ritonavir adverse effects. After 3 days of ritonavir 400 mg twice daily plus moxifloxacin (400 mg once daily), ritonavir exposure was approximately 1.5 times higher than exposure that has been observed with ritonavir 600 mg twice-daily alone. Caution and close monitoring is advised if these drugs are administered together. [\[47165\]](#) [\[60002\]](#)

Nabilone: (Moderate) Coadministration of ritonavir and oral THC results in increased THC concentrations. A decreased dose of nabilone may be needed if these drugs are coadministered with ritonavir. [\[5044\]](#)

Nadolol: (Moderate) Cardiac and neurologic events have been reported when ritonavir was concurrently administered with beta-blockers. [\[5044\]](#)

Nafcillin: (Major) Concurrent administration of nafcillin with ritonavir may result in decreased plasma concentrations of ritonavir, which may affect antiviral efficacy. Nafcillin is an inducer of the hepatic isoenzyme CYP3A4; ritonavir is a CYP3A4 substrate. Caution and close monitoring are advised if these drugs are administered together. [\[11312\]](#) [\[11313\]](#) [\[58664\]](#)

Naldemedine: (Major) Monitor for potential naldemedine-related adverse reactions if coadministered with ritonavir. The plasma concentrations of naldemedine may be increased during concurrent use. Naldemedine is a substrate of CYP3A4 and P-gp; ritonavir is a moderate P-gp inhibitor and a strong CYP3A4 inhibitor. [\[28380\]](#) [\[34557\]](#) [\[47165\]](#) [\[61831\]](#)

Naloxegol: (Severe) Concomitant use of naloxegol with ritonavir is contraindicated. Naloxegol is metabolized primarily by CYP3A. Strong CYP3A4 inhibitors, such as ritonavir, can significantly increase exposure to naloxegol which may precipitate opioid withdrawal symptoms such as hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning. [\[47165\]](#) [\[57937\]](#)

Nateglinide: (Moderate) Concurrent administration of nateglinide with some protease inhibitors may result in elevated nateglinide plasma concentrations via inhibition of CYP2C9. Ritonavir may induce CYP2C9 leading to a reduction of nateglinide concentrations. Monitor blood glucose concentrations during coadministration as hypoglycemia or hyperglycemia could occur. New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Monitor blood glucose concentrations during coadministration. Caution and close monitoring are advised if these drugs are administered together. [\[30585\]](#) [\[45644\]](#) [\[47165\]](#)

Nebivolol: (Moderate) Ritonavir is expected to decrease the hepatic CYP metabolism of beta-blockers like nebivolol, resulting in increased beta-blocker concentrations. Cardiac and neurologic events have been reported when ritonavir is concurrently administered with beta-blockers. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including beta-blockers) has not been evaluated. If coadministration of nebivolol and ritonavir is warranted, do so with caution and careful monitoring. Decreased beta-blocker doses may be warranted. [\[28315\]](#) [\[60860\]](#)

Nebivolol; Valsartan: (Moderate) Concurrent use of lopinavir with valsartan may result in elevated valsartan serum concentrations. Valsartan is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. Monitor for increased toxicities if these drugs are given together. [\[56575\]](#) [\[61510\]](#) [\[61511\]](#) [\[61513\]](#) (Moderate) Ritonavir is expected to decrease the hepatic CYP metabolism of beta-blockers like nebivolol, resulting in increased beta-blocker concentrations. Cardiac and neurologic events have been reported when ritonavir is concurrently administered with beta-blockers. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including beta-blockers) has not been evaluated. If coadministration of nebivolol and ritonavir is warranted, do so with caution and careful monitoring. Decreased beta-blocker doses may be warranted. [\[28315\]](#) [\[60860\]](#) (Minor) Valsartan is a substrate of the hepatic efflux transporter MRP2 and ritonavir is an inhibitor of MRP2. Coadministration may increase systemic exposure to valsartan. Patients should be monitored for adverse effects of valsartan during coadministration. [\[28315\]](#) [\[29130\]](#) [\[36646\]](#) [\[39870\]](#) [\[60860\]](#)

Nefazodone: (Major) Elevated plasma concentrations of nefazodone and ritonavir may occur. Both ritonavir and nefazodone are CYP3A4 substrates/potent inhibitors. Cardiac and neurologic events have been reported when ritonavir was concurrently administered with nefazodone. If coadministration of these drugs is warranted, do so with caution and careful monitoring. A 50% reduction in the nefazodone dose may be warranted. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs with potential bradycardic effects has not been evaluated. [\[28315\]](#) [\[47165\]](#) [\[4718\]](#) [\[5044\]](#) [\[5414\]](#) [\[54634\]](#) [\[5772\]](#) (Major) Lopinavir; ritonavir may inhibit the CYP3A metabolism of nefazodone, and necessitate up to a 50% reduction in nefazodone dose. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of lopinavir; ritonavir with other drugs with potential bradycardic effects has not been evaluated. Close monitoring of nefazodone concentrations and/or therapeutic and adverse effects would be prudent. Additionally, caution is warranted, as cardiac and neurologic events have been reported when ritonavir and nefazodone are used concomitantly. [\[28341\]](#) [\[54634\]](#)

Nelfinavir: (Major) Coadministration of lopinavir; ritonavir and nelfinavir may result in decreased concentrations of lopinavir. If coadministered, the dose of lopinavir; ritonavir must be increased and given twice daily; do not use once daily administration. Consult dosing information for recommended adjustments. [\[28341\]](#) (Moderate) Concurrent administration of ritonavir and nelfinavir results in a 1.5-fold increase of nelfinavir AUC. Dosage recommendations for coadministration from HIV treatment guidelines are ritonavir 400 mg twice daily plus nelfinavir 500 to 750 mg twice daily. Both ritonavir and nelfinavir are potent inhibitors and substrates of CYP3A4 and P-glycoprotein (P-gp). [\[11417\]](#) [\[11418\]](#) [\[28839\]](#) [\[46638\]](#)

Neratinib: (Major) Avoid concomitant use of ritonavir with neratinib due to an increased risk of neratinib-related toxicity. Neratinib is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased neratinib exposure by 381%; concomitant use with other strong inhibitors of CYP3A4 may also increase neratinib concentrations. [\[47165\]](#) [\[62127\]](#)

Netupitant; Fosnetupitant; Palonosetron: (Major) Netupitant is a moderate inhibitor of CYP3A4 and should be used with caution in patients receiving concomitant medications that are metabolized through CYP3A4 such as lopinavir; ritonavir; the inhibitory effect on CYP3A4 can last for multiple days. Increased lopinavir or ritonavir concentrations may occur and may lead to ritonavir-induced side effects, including a possible risk for QT prolongation. In addition, netupitant is mainly metabolized by CYP3A4. Coadministration of netupitant; palonosetron with a strong CYP3A4 inhibitor such as ritonavir can significantly increase the systemic exposure to netupitant. No dosage adjustment is necessary for single dose administration of netupitant; palonosetron. [\[28341\]](#) [\[58171\]](#) (Moderate) Coadministration may result in increased netupitant and ritonavir exposure. Netupitant is a CYP3A4 substrate and moderate inhibitor of CYP3A4; the inhibitory effect on CYP3A4 can last for multiple days. Ritonavir is a CYP3A4 substrate and strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased netupitant exposure by 140%. No dosage adjustment is necessary. [\[47165\]](#) [\[58171\]](#)

Nevirapine: (Major) Coadministration of lopinavir; ritonavir and nevirapine may result in decreased concentrations of lopinavir. If coadministered, the dose of lopinavir; ritonavir must be increased and given twice daily; do not use once daily administration. Consult dosing information for recommended adjustments. [\[28341\]](#) (Moderate) Concurrent administration of nevirapine with ritonavir may result in elevated nevirapine plasma concentrations and decreased concentrations of ritonavir. Nevirapine is a substrate and inducer of the

hepatic isoenzyme CYP3A4; ritonavir is a substrate and potent inhibitor of this enzyme. Caution and close monitoring for antiviral efficacy and adverse effects are advised if these drugs are administered together. [5222] [58664]

Niacin; Simvastatin: (Severe) The coadministration of anti-retroviral protease inhibitors with simvastatin is contraindicated. Taking these drugs together may significantly increase the serum concentration of simvastatin; thereby increasing the risk of myopathy and rhabdomyolysis. One report has demonstrated that ritonavir plus saquinavir therapy markedly increases the AUC for simvastatin by 3059%. Simvastatin is a substrate for CYP3A4 and the drug transporter organic anion transporting polypeptide (OATP1B1); protease inhibitors are CYP3A4 and OATP inhibitors. [28605] [39682] [46638] [61510] [61511] [61512] [61513]

Nicardipine: (Moderate) Anti-retroviral protease inhibitors may decrease the hepatic CYP metabolism of calcium-channel blockers (mainly through CYP3A4 inhibition) resulting in increased calcium-channel blocker concentrations. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [11537] [28315] [47165] [50341] [56565]

Nifedipine: (Major) According to the manufacturer of nifedipine, coadministration with ritonavir may result in increased exposure to nifedipine, and initiation of nifedipine should begin with the lowest available dose. Anti-retroviral protease inhibitors may decrease the hepatic CYP metabolism of calcium-channel blockers (mainly through CYP3A4 inhibition) resulting in increased calcium-channel blocker concentrations. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [28315] [29068] [31749] (Major) Lopinavir; ritonavir (Kaletra) may decrease the clearance of calcium-channel blockers via inhibition of CYP3A4 metabolism. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of lopinavir; ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. Caution is warranted and clinical monitoring of the patient is recommended. [28341] [29068] [31749]

Nilotinib: (Major) Avoid coadministration of lopinavir with nilotinib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Sudden death and QT interval prolongation have occurred in patients who received nilotinib therapy. [28341] [58766] [65157] [65170] (Major) Avoid the concomitant use of nilotinib and ritonavir. If coadministration is required, monitor patients closely for prolongation of the QT interval and reduce the nilotinib dose to 300 mg once daily in patients with resistant or intolerant Ph+ CML or to 200 mg once daily in patients with newly diagnosed Ph+ CML. If ritonavir is discontinued, a washout period should be allowed before adjusting the nilotinib dosage upward to the indicated dose. Nilotinib is a substrate and moderate inhibitor of CYP3A4 and ritonavir is a substrate and a strong inhibitor of CYP3A4. [28315] [47165] [58766]

Nimodipine: (Moderate) Anti-retroviral protease inhibitors are CYP3A4 inhibitors and may decrease the hepatic metabolism of nimodipine, leading to increased plasma concentrations of nimodipine. In addition, ritonavir and calcium channel blockers both prolong the PR interval and the manufacturer for ritonavir recommends caution during coadministration. Monitor therapeutic response and for adverse effects, such as hypotension. Decreased calcium-channel blocker doses may be warranted. [28315] [29082] [32432] [47165]

Nintedanib: (Moderate) Dual inhibitors of P-glycoprotein (P-gp) and CYP3A4, such as ritonavir, are expected to increase the exposure and clinical effect of nintedanib. If use together is necessary, closely monitor for increased nintedanib side effects including gastrointestinal toxicity (nausea, vomiting, diarrhea, abdominal pain, loss of appetite), headache, elevated liver enzymes, and hypertension. A dose reduction, interruption of therapy, or discontinuation of nintedanib therapy may be necessary. Ritonavir is a potent CYP3A4 inhibitor and a P-gp inhibitor; nintedanib is a P-gp substrate and a minor CYP3A4 substrate. In drug interactions studies, administration of nintedanib with a dual P-gp and CYP3A4 inhibitor increased nintedanib AUC by 60%. [28341] [38968] [47165] [58203]

Nisoldipine: (Moderate) Anti-retroviral protease inhibitors may decrease the hepatic CYP metabolism of calcium-channel blockers (mainly through CYP3A4 inhibition) resulting in increased calcium-channel blocker concentrations. In addition, ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [28315] [32432] [47165]

Norethindrone: (Moderate) Many anti-retroviral protease inhibitors may interact with hormonal agents like norethindrone, due to their actions on CYP metabolism, particularly CYP3A4. Data on the effects that protease inhibitors have on the serum concentrations of norethindrone are complex and are based mostly off of data with norethindrone-containing contraceptives. For example, ritonavir (also found in combinations like lopinavir; ritonavir, and used as a booster in many HIV treatment regimens) may decrease the metabolism of norethindrone, raising norethindrone concentrations. Women receiving norethindrone for hormone replacement or contraception should report potential hormonal adverse effects (e.g., bleeding pattern changes, acne, emotional lability) or any changes in efficacy (e.g., noted changes in bleeding patterns) to their prescribers. Because norethindrone-containing contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive norethindrone contraception concurrently with ritonavir should use an additional barrier method of contraception such as condoms. [58679] [7731]

Norfloxacin: (Major) Avoid coadministration of lopinavir with norfloxacin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Quinolones have been associated with a risk of QT prolongation and torsade de pointes (TdP). Although extremely rare, TdP has been reported during postmarketing surveillance of norfloxacin. These reports generally involved patients with concurrent medical conditions or concomitant medications that may have been contributory. [28225] [28341] [28432] [28457] [29818] [65157] [65170]

Nortriptyline: (Moderate) A dose reduction of the tricyclic antidepressant (TCA) may be necessary when coadministered with ritonavir. Concurrent use may result in elevated TCA plasma concentrations. [47165]

Octreotide: (Major) Avoid coadministration of lopinavir with octreotide due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Arrhythmias, sinus bradycardia, and conduction disturbances have occurred during octreotide therapy. Since bradycardia is a risk factor for development of torsade de pointes (TdP), the potential occurrence of bradycardia during octreotide administration could theoretically increase the risk of TdP in patients receiving drugs that prolong the QT interval. [28341] [4951] [65157] [65170]

Ofloxacin: (Major) Avoid coadministration of lopinavir with ofloxacin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Quinolones have been associated with a risk of QT prolongation and torsade de pointes (TdP). Although extremely rare, TdP has been reported during postmarketing surveillance of ofloxacin. These reports generally involved patients with concurrent medical conditions or concomitant medications that may have been contributory. [28341] [30738] [65157] [65170]

Olanzapine: (Major) Avoid coadministration of lopinavir with olanzapine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Limited data, including some case reports, suggest that olanzapine may be associated with a significant prolongation of the QTc interval. [28341] [28785] [32732] [32734] [32745] [32746] [65157] [65170] (Moderate) Ritonavir may reduce olanzapine serum concentrations by approximately 50%; how this affects olanzapine efficacy, however, is not known. Ritonavir appears to induce olanzapine's metabolism by either CYP1A2 or glucuronide conjugation. If ritonavir and olanzapine are used concurrently, monitor for reduced olanzapine effect and adjust olanzapine dose as needed. [27275]

Olaparib: (Major) Avoid coadministration of olaparib with ritonavir due to the risk of increased olaparib-related adverse reactions. If concomitant use is unavoidable, reduce the dose of olaparib to 100 mg twice daily; the original dose may be resumed 3 to 5 elimination half-lives after ritonavir is discontinued. Olaparib is a CYP3A substrate and ritonavir is a strong CYP3A4 inhibitor; concomitant use may increase olaparib exposure. Coadministration with another strong CYP3A inhibitor increased the olaparib C_{max} by 42% and the AUC by 170%. [28380] [34557] [47165] [58662]

Olodaterol: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28318] [28341] [32901] [33925] [41231] [65157] [65170] (Moderate) Beta-agonists, such as olodaterol, may be associated with adverse cardiovascular effects including QT interval prolongation. Beta-agonists should be administered with extreme caution to patients being treated with drugs known to prolong the QT interval because the action of beta-agonists on the cardiovascular system may be potentiated. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with olodaterol include ritonavir. [47165] [57710]

Ombitasvir; Paritaprevir; Ritonavir: (Major) Avoid coadministration of lopinavir with paritaprevir. Use of these drugs in combination has resulted in elevated paritaprevir serum concentrations. Paritaprevir is a substrate of the drugs transporter organic anion transporting polypeptide (OATP1B1); lopinavir is an OATP1B1 inhibitor. [58664] [61510] [61511] [61513]

Omeprazole: (Moderate) Increased exposure to omeprazole may occur during concurrent administration of ritonavir. Although dosage adjustment of omeprazole is not normally required, dosage reduction may be considered in patients receiving higher omeprazole doses (e.g., those with Zollinger-Ellison syndrome). Ritonavir is a strong CYP3A4 inhibitor. Omeprazole is a CYP2C19 and CYP3A4 substrate. Coadministration of a dual CYP2C19/strong CYP3A4 inhibitor increased the omeprazole AUC by an average of 4-times. [29564] [47165]

Omeprazole; Amoxicillin; Rifabutin: (Major) Coadministration of ritonavir and rifabutin results in clinically significant alterations of rifabutin pharmacokinetic parameters, with the rifabutin AUC being increased by 430%. In patients receiving any dosage of ritonavir, the dose of rifabutin should always be decreased to 150 mg every day or 300 mg three times per week. [46638] (Major) Coadministration with lopinavir; ritonavir (Kaletra) results in clinically significant alterations in rifabutin pharmacokinetics; the AUC increases by more than 300% and the metabolite, 25-O-des-acetyl-rifabutin, AUC increases by 47.5 fold. If these drugs are coadministered, the CDC recommends the adult dose of rifabutin be reduced to 150 mg every day or 300 mg three times per week. Increased monitoring for adverse reactions is warranted. [28341] [46638] (Moderate) Increased exposure to omeprazole may occur during concurrent administration of ritonavir. Although dosage adjustment of omeprazole is not normally required, dosage reduction may be considered in patients receiving higher omeprazole doses (e.g., those with Zollinger-Ellison syndrome). Ritonavir is a strong CYP3A4 inhibitor. Omeprazole is a CYP2C19 and CYP3A4 substrate. Coadministration of a dual CYP2C19/strong CYP3A4 inhibitor increased the omeprazole AUC by an average of 4-times. [29564] [47165]

Omeprazole; Sodium Bicarbonate: (Moderate) Concurrent administration of tipranavir and ritonavir with antacids results in decreased tipranavir concentrations. Administer tipranavir and ritonavir 2 hours before or 1 hour after antacids. [1800] [1802] (Moderate) Increased exposure to omeprazole may occur during concurrent administration of ritonavir. Although dosage adjustment of omeprazole is not normally required, dosage reduction may be considered in patients receiving higher omeprazole doses (e.g., those with Zollinger-Ellison syndrome). Ritonavir is a strong CYP3A4 inhibitor. Omeprazole is a CYP2C19 and CYP3A4 substrate. Coadministration of a dual CYP2C19/strong CYP3A4 inhibitor increased the omeprazole AUC by an average of 4-times. [29564] [47165]

Ondansetron: (Major) Avoid coadministration of lopinavir with ondansetron due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Ondansetron has been associated with a dose-related increase in the QT interval and postmarketing reports of torsade de pointes (TdP). [28341] [31266] [65157] [65170] (Moderate) Caution and close monitoring are advised if these drugs are administered together. Ondansetron exposure may be altered resulting in increased adverse effects or decreased efficacy. Ondansetron is metabolized by the hepatic isoenzymes CYP3A4, CYP2D6, and CYP1A2; ritonavir inhibits CYP3A4 and CYP2D6 and induces CYP1A2. [31266] [47165]

Oritavancin: (Major) Lopinavir; ritonavir is metabolized by CYP3A4; oritavancin is a weak CYP3A4 inducer. Plasma concentrations and efficacy of lopinavir; ritonavir may be reduced if these drugs are administered concurrently. [27493] [27494] [28341] [57741] (Major) Ritonavir is metabolized by CYP3A4 and CYP2D6 (minor); oritavancin is a weak CYP3A4 and CYP2D6 inducer. Plasma concentrations and efficacy of ritonavir may be reduced if these drugs are administered concurrently. [27493] [27494] [34557] [57741]

Orlistat: (Major) According to the manufacturer of orlistat, HIV RNA levels should be frequently monitored in patients receiving orlistat while being treated for HIV infection with anti-retroviral protease inhibitors. Loss of virological control has been reported in HIV-infected patients taking orlistat with atazanavir, ritonavir, tenofovir disoproxil fumarate, emtricitabine, lopinavir; ritonavir, and emtricitabine; efavirenz; tenofovir disoproxil fumarate. The exact mechanism for this interaction is not known, but may involve inhibition of systemic absorption of the anti-retroviral agent. If an increased HIV viral load is confirmed, orlistat should be discontinued. [27971]

Osilodrostat: (Major) Avoid coadministration of lopinavir with osilodrostat due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Osilodrostat is associated with dose-dependent QT prolongation. [28341] [65098] [65157] [65170] (Major) Reduce the dose of osilodrostat by one-half during coadministration of ritonavir; concurrent use may increase osilodrostat exposure and the risk of osilodrostat-related adverse reactions. Osilodrostat is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. [47165] [65098]

Osimertinib: (Major) Avoid coadministration of lopinavir with osimertinib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Interrupt or dose reduce osimertinib if QT prolongation occurs. Concentration-dependent QTc prolongation occurred during clinical trials of osimertinib. Lopinavir is associated with QT prolongation. [28341] [60297] [65157] [65170]

Ospemifene: (Major) Use caution when administering ospemifene to a patient taking ritonavir, as concurrent use may increase ospemifene systemic exposure and increase the risk of ospemifene-related adverse reactions. Consider if alternative therapy is appropriate. Ritonavir is a strong CYP3A4 inhibitor and a CYP2C9 inhibitor, and ospemifene is a CYP3A4 and CYP2C9 substrate. Co-administration of ospemifene with a drug known to inhibit CYP3A4 and CYP2C9 isoenzymes increased the ospemifene exposure 2.7-fold. [47165] [53344]

Oxaliplatin: (Major) Avoid coadministration of lopinavir with oxaliplatin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. QT prolongation and ventricular arrhythmias including fatal torsade de pointes have been reported with oxaliplatin use in postmarketing experience. [28341] [41958] [65157] [65170]

Oxcarbazepine: (Major) Concurrent administration of oxcarbazepine with ritonavir should be undertaken with caution and careful monitoring of antiviral efficacy. Oxcarbazepine is a moderate inducer of the hepatic isoenzyme CYP3A4, and ritonavir is a CYP3A4 substrate. [29014] [58664]

Oxybutynin: (Moderate) Oxybutynin is metabolized by CYP3A4. Caution should be used when oxybutynin is given in combination with inhibitors of CYP3A4, such as protease inhibitors. Monitor for adverse effects if these drugs are administered together. [29796] [47165] [58664]

Oxycodone: (Moderate) Consider a reduced dose of oxycodone with frequent monitoring for respiratory depression and sedation if concurrent use of ritonavir is necessary. If ritonavir is discontinued, consider increasing the oxycodone dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oxycodone is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like ritonavir can increase oxycodone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of oxycodone. If ritonavir is discontinued, oxycodone plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to oxycodone. [39926] [47165]

Oxymorphone: (Moderate) Ritonavir is an inhibitor of the cytochrome P450 3A4 isoenzyme and may decrease the metabolism of oxymorphone if the two drugs are coadministered. [4718]

Paclitaxel: (Minor) Due to ritonavir's potential inhibitory effects on various hepatic isoenzymes, numerous drug interactions may occur with ritonavir. Close monitoring of serum drug concentrations and/or therapeutic and adverse effects is required when paclitaxel (a CYP2C8 and CYP3A4 substrate) is coadministered with ritonavir (a CYP3A4 inhibitor). In addition, paclitaxel is a substrate of the drug transporter P-glycoprotein (P-gp), and ritonavir also inhibits P-gp. [28001] [28341] [28380] [28498] [49806] [56579] [58664]

Palbociclib: (Major) Avoid coadministration of lopinavir with palbociclib; significantly increased palbociclib exposure may occur. Concentrations of lopinavir may also increase. If concomitant use cannot be avoided, reduce the dose of palbociclib to 75 mg PO once daily and monitor for increased adverse reactions. If lopinavir is discontinued, increase the palbociclib dose (after 3 to 5 half-lives) to the dose used before initiation of lopinavir. Palbociclib is primarily metabolized by CYP3A4 and lopinavir is a strong CYP3A4 inhibitor. In a drug interaction trial, coadministration with another strong CYP3A4 inhibitor increased the AUC and Cmax of palbociclib by 87% and 34%, respectively. Palbociclib is also a weak time-dependent inhibitor of CYP3A and lopinavir is a sensitive CYP3A4 substrate. [28341] [56579] [58768] [64721] (Major) Avoid coadministration of ritonavir with palbociclib; significantly increased plasma exposure of palbociclib may occur. If concomitant use cannot be avoided, reduce the dose of palbociclib to 75 mg PO once daily and monitor for increased adverse reactions. If ritonavir is discontinued, increase the palbociclib dose (after 3 to 5 half-lives of ritonavir) to the dose used before initiation of ritonavir. Palbociclib is primarily metabolized by CYP3A4 and ritonavir is a strong CYP3A4 inhibitor. In a drug interaction trial, coadministration with another strong CYP3A4 inhibitor increased the AUC and Cmax of palbociclib by 87% and 34%, respectively. [47165] [58768] [64721]

Paliperidone: (Major) Avoid coadministration of lopinavir with paliperidone due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid

any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Paliperidone has been associated with QT prolongation; torsade de pointes and ventricular fibrillation have been reported in the setting of overdose. [\[28341\]](#) [\[40936\]](#) [\[65157\]](#) [\[65170\]](#)

Panobinostat: (Major) Avoid coadministration of lopinavir with panobinostat due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [\[28341\]](#) [\[58821\]](#) [\[65157\]](#) [\[65170\]](#) (Major) Reduce the starting dose of panobinostat to 10 mg when coadministered with ritonavir. Concurrent use may increase systemic exposure of panobinostat. Panobinostat is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration of another strong CYP3A4 inhibitor increased the AUC of panobinostat by 73%. [\[47165\]](#) [\[58821\]](#)

Paricalcitol: (Moderate) Paricalcitol is partially metabolized by CYP3A4. Care should be taken when dosing paricalcitol with strong CYP3A4 inhibitors, such as protease inhibitors. Dose adjustments of paricalcitol may be required. Monitor plasma PTH and serum calcium and phosphorous concentrations if a patient initiates or discontinues therapy with this combination. [\[42290\]](#)

Paroxetine: (Major) A dose reduction of paroxetine may be necessary during co-administration of ritonavir. Concurrent use of CYP2D6 substrates, such as paroxetine, with ritonavir could result in increases (up to 2-fold) in the AUC of paroxetine. Paroxetine is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [\[28260\]](#) [\[60002\]](#)

Pasireotide: (Major) Avoid coadministration of lopinavir with pasireotide due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. QT prolongation has occurred with pasireotide at therapeutic and supratherapeutic doses. [\[28341\]](#) [\[52611\]](#) [\[65157\]](#) [\[65170\]](#)

Pazopanib: (Major) Avoid coadministration of lopinavir with pazopanib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [\[28341\]](#) [\[37098\]](#) [\[65157\]](#) [\[65170\]](#) (Major) Avoid coadministration of pazopanib and ritonavir due to the potential for increased pazopanib exposure. If concurrent use is unavoidable, reduce the pazopanib dose to 400 mg PO once daily; further dose adjustments may be necessary if adverse effects occur. Pazopanib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Concurrent use of another strong CYP3A4 inhibitor increased the C_{max} and AUC of pazopanib by 1.5-fold and 1.7-fold, respectively. [\[37098\]](#) [\[47165\]](#)

Penbutolol: (Moderate) Cardiac and neurologic events have been reported when ritonavir was concurrently administered with beta-blockers. [\[5044\]](#)

Pentamidine: (Major) Avoid coadministration of lopinavir with systemic pentamidine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Systemic pentamidine and lopinavir have been associated with QT prolongation. [\[23620\]](#) [\[23778\]](#) [\[28341\]](#) [\[28419\]](#) [\[28879\]](#) [\[65157\]](#) [\[65170\]](#)

Pentobarbital: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [\[28341\]](#) [\[46638\]](#) (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [\[46638\]](#)

Perampanel: (Moderate) Concurrent use of perampanel with ritonavir may decrease ritonavir concentrations and increase perampanel concentrations. Both drugs are metabolized by CYP3A4. Ritonavir is also a CYP3A4 inhibitor, while perampanel is a weak inducer of CYP3A4. Monitor patients for increases in adverse effects such as anger, anxiety, irritability, somnolence, dizziness, or nausea. Dose adjustment may be required. [\[51834\]](#) [\[52140\]](#)

Pergolide: (Severe) Coadministration of ergot alkaloids with potent inhibitors of CYP3A4, like anti-retroviral protease inhibitors is considered contraindicated due to the risk of acute ergot toxicity (e.g., vasospasm leading to cerebral ischemia, peripheral ischemia and/or other serious effects). Several case reports have established the clinical significance of this interaction in the medical literature. In some cases, fatal interactions have occurred. [\[28142\]](#) [\[28341\]](#) [\[28731\]](#) [\[28839\]](#) [\[28995\]](#) [\[32432\]](#) [\[46638\]](#) [\[5018\]](#) [\[5044\]](#) [\[5623\]](#) [\[5747\]](#) [\[8102\]](#)

Perindopril; Amlodipine: (Moderate) Amlodipine is a CYP3A4 substrate. Theoretically, CYP3A4 inhibitors, such as anti-retroviral protease inhibitors, may increase the plasma concentration of amlodipine via CYP3A4 inhibition; this effect might lead to hypotension in some individuals. Caution should be used when anti-retroviral protease inhibitors are coadministered with amlodipine; therapeutic response should be monitored. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [\[29090\]](#) [\[47165\]](#) [\[58664\]](#)

Perphenazine: (Major) Avoid coadministration of lopinavir with perphenazine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Perphenazine is associated with a possible risk for QT prolongation. [\[28341\]](#) [\[28415\]](#) [\[65157\]](#) [\[65170\]](#)

Perphenazine; Amitriptyline: (Major) Avoid coadministration of lopinavir with perphenazine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Perphenazine is associated with a possible risk for QT prolongation. [28341] [28415] [65157] [65170] (Moderate) A dose reduction of the tricyclic antidepressant (TCA) may be necessary when coadministered with ritonavir. Concurrent use may result in elevated TCA plasma concentrations. [47165]

Pexidartinib: (Major) Avoid coadministration of pexidartinib with ritonavir as concurrent use may increase pexidartinib exposure. If concurrent use cannot be avoided, reduce the dose of pexidartinib. If ritonavir is discontinued, increase the pexidartinib dose to the original dose after 3 plasma half-lives of ritonavir. Dose adjustments are as follows: 800 mg/day or 600 mg/day of pexidartinib, reduce to 200 mg twice daily; 400 mg/day of pexidartinib, reduce to 200 mg once daily. Pexidartinib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration of another strong CYP3A4 inhibitor increased pexidartinib exposure by 70%. [47165] [64535]

Phenobarbital: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [28341] [46638] (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [46638]

Phentermine; Topiramate: (Moderate) Concurrent administration of topiramate with ritonavir may result in decreased concentrations of ritonavir. Topiramate is not extensively metabolized, but is a mild CYP3A4 inducer. Ritonavir is metabolized by this enzyme. Caution and close monitoring are advised if these drugs are administered together. [28378] [57036] [58664]

Phenylephrine; Promethazine: (Major) Avoid coadministration of lopinavir with promethazine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Promethazine, a phenothiazine, is also associated with a possible risk for QT prolongation. [28225] [28341] [55578] [65157] [65170]

Phenytoin: (Major) Concurrent use of ritonavir with ethosuximide, phenytoin, or fosphenytoin should be avoided when possible. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. Additionally, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [28315] [46638]

Pimavanserin: (Major) Avoid coadministration of lopinavir with pimavanserin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs are associated with QT prolongation. [28341] [60748] [65157] [65170] (Major) Reduce the dose of pimavanserin to 10 mg PO once daily and monitor for pimavanserin-related adverse reactions, including nausea, vomiting, confusion, loss of balance or coordination, and QT prolongation if coadministration with ritonavir is necessary. Concurrent use may increase pimavanserin exposure. Pimavanserin is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. In drug interaction studies, coadministration with a strong CYP3A4 inhibitor increased exposure to pimavanserin by 3-fold. [47165] [60748]

Pimozide: (Severe) Coadministration of pimozide with protease inhibitors is contraindicated due to the risk of life threatening arrhythmias such as torsade de pointes (TdP). Pimozide is thought to be metabolized through CYP3A4, and to a lesser extent CYP1A2 and CYP2D6. Elevated pimozide plasma levels are probable when coadministered with CYP450 inhibitors, such as the protease inhibitors. Increased plasma concentrations of pimozide have been associated with QT prolongation and serious cardiovascular adverse events including death due to TdP. [43463]

Pindolol: (Moderate) Ritonavir is expected to decrease the hepatic CYP metabolism of pindolol, resulting in increased beta-blocker concentrations. Cardiac and neurologic events have been reported when ritonavir is concurrently administered with beta-blockers. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including beta-blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased beta-blocker doses may be warranted. [28315]

Pirbuterol: (Major) Avoid coadministration of lopinavir with short-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28341] [33925] [65157] [65170]

Pirfenidone: (Moderate) Concurrent administration of pirfenidone with ritonavir may result in elevated plasma concentrations of ritonavir. Pirfenidone is a mild inhibitor of CYP3A4 and the drug transporter P-glycoprotein (P-gp); ritonavir is a substrate of both CYP3A4 and P-gp. Monitor for antiviral adverse effects if these drugs are administered together. [58189] [58664]

Pitolisant: (Major) Avoid coadministration of lopinavir with pitolisant due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [28341] [64562] [65157] [65170]

Polatuzumab Vedotin: (Moderate) Monitor for increased polatuzumab vedotin toxicity during coadministration of ritonavir due to the risk of elevated exposure to the cytotoxic component of polatuzumab vedotin, MMAE. MMAE is metabolized by CYP3A4; ritonavir is a strong CYP3A4 inhibitor. Strong CYP3A4 inhibitors are predicted to increase the exposure of MMAE by 45%. [\[47165\]](#) [\[64290\]](#)

Pomalidomide: (Moderate) Use pomalidomide and ritonavir together with caution; decreased pomalidomide exposure may occur resulting in reduced pomalidomide effectiveness. Pomalidomide is a CYP1A2 substrate and ritonavir is a CYP1A2 inducer. [\[28315\]](#) [\[59487\]](#)

Ponatinib: (Major) Concomitant use of ponatinib, a CYP3A4 substrate, and ritonavir, a strong CYP3A4 inhibitor, may increase the exposure of ponatinib. If the use of both agents is necessary, reduce the starting ponatinib dose to 30 mg/day. Additionally, ponatinib is a P-gp inhibitor and may increase the plasma concentration of a P-gp substrate such as, ritonavir. [\[11416\]](#) [\[28315\]](#) [\[5110\]](#) [\[52603\]](#)

Posaconazole: (Major) Avoid coadministration of lopinavir with posaconazole due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Posaconazole has been associated with prolongation of the QT interval as well as rare cases of torsade de pointes (TdP). [\[28341\]](#) [\[32723\]](#) [\[65157\]](#) [\[65170\]](#) (Moderate) Perform frequent monitoring of adverse effects and toxicity of ritonavir during coadministration with posaconazole. These drugs used in combination may result in elevated ritonavir plasma concentrations, causing an increased risk for ritonavir-related adverse events. Data from one study found the C_{max} and AUC of ritonavir increased by 49% and 80%, respectively, when administered with posaconazole. [\[32723\]](#)

Pramlintide: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. [\[30575\]](#) [\[51227\]](#)

Praziquantel: (Moderate) Monitor for increased side effects of praziquantel if administered with ritonavir. Concurrent administration may result in elevated praziquantel plasma concentrations. Praziquantel is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. [\[27480\]](#) [\[34457\]](#) [\[34458\]](#) [\[34459\]](#) [\[47165\]](#) [\[58664\]](#)

Prednisolone: (Moderate) Ritonavir inhibits CYP3A4, and prednisolone is a CYP3A4 substrate. Monitor patients for corticosteroid-related side effects if prednisone or prednisolone and ritonavir are taken. [\[4194\]](#) [\[58664\]](#)

Prednisone: (Moderate) Coadministration of prednisone with ritonavir (a strong CYP3A4 inhibitor) may cause prednisone serum concentrations to increase, potentially resulting in Cushing's syndrome and adrenal suppression. Consider use of an alternative corticosteroid whose concentrations are less affected by strong CYP3A4 inhibitors, such as beclomethasone and prednisolone, especially during long-term treatment. [\[47165\]](#) [\[58664\]](#)

Primaquine: (Major) Avoid coadministration of lopinavir with primaquine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs are associated with QT prolongation. [\[28341\]](#) [\[41984\]](#) [\[65157\]](#) [\[65170\]](#)

Primidone: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [\[28341\]](#) [\[46638\]](#) (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [\[46638\]](#)

Procainamide: (Major) Avoid coadministration of lopinavir with procainamide due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Procainamide is associated with a well-established risk of QT prolongation and torsade de pointes (TdP). [\[28250\]](#) [\[28341\]](#) [\[65157\]](#) [\[65170\]](#)

Prochlorperazine: (Major) Avoid coadministration of lopinavir with prochlorperazine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Prochlorperazine is associated with a possible risk for QT prolongation. [\[28225\]](#) [\[28341\]](#) [\[28415\]](#) [\[65157\]](#) [\[65170\]](#)

Promethazine: (Major) Avoid coadministration of lopinavir with promethazine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Promethazine, a phenothiazine, is also associated with a possible risk for QT prolongation. [\[28225\]](#) [\[28341\]](#) [\[55578\]](#) [\[65157\]](#) [\[65170\]](#)

Propafenone: (Major) Avoid coadministration of lopinavir with propafenone due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Propafenone is a Class IC antiarrhythmic which increases the QT interval, but largely due to prolongation of the QRS interval. [\[28287\]](#) [\[28341\]](#) [\[65157\]](#) [\[65170\]](#) (Major) Coadministration of HIV treatment doses of ritonavir and propafenone is contraindicated due to the potential for serious or life-threatening reactions, such as cardiac arrhythmias. However, propafenone and ritonavir may be coadministered with caution to patients receiving ritonavir as a boosting agent. Ritonavir inhibits both CYP3A4 and CYP2D6. Drugs that inhibit both pathways are expected to increase propafenone serum concentrations. [\[28287\]](#) [\[28315\]](#) [\[46638\]](#) [\[58664\]](#)

Propofol: (Moderate) Use caution if ritonavir is coadministered with propofol due to the potential for decreased propofol exposure which may decrease its efficacy. Propofol is a CYP2B6 substrate and ritonavir is a CYP2B6 inducer. [47165] [65210] [65225]

Propoxyphene: (Moderate) Due to effects on microsomal isoenzymes responsible for hepatic metabolism, ritonavir may alter the response and/or increase the AUC of opiate analgesics. Concurrent use of ritonavir and propoxyphene is not recommended, due the increased formation of the neurotoxic metabolites of propoxyphene. Also, propoxyphene is a substrate/inhibitor of CYP3A4. Increased serum concentrations of propoxyphene can occur from concurrent use of ritonavir, a CYP3A4 inhibitor. A reduced dosage of propoxyphene may be needed. Monitor for CNS and respiratory depression. [11379] [36008] [4718] [5044]

Propranolol: (Moderate) Concurrent administration of propranolol with ritonavir may result in elevated propranolol plasma concentrations. Cardiac and neurologic events have been reported when ritonavir is concurrently administered with beta-blockers. Propranolol is metabolized by the hepatic isoenzyme CYP2D6; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. Decreased beta-blocker dosage may be needed. [28315] [47165] [4998] [58664]

Protriptyline: (Moderate) A dose reduction of the tricyclic antidepressant (TCA) may be necessary when coadministered with ritonavir. Concurrent use may result in elevated TCA plasma concentrations. [47165]

Quazepam: (Major) CYP3A4 inhibitors, such as protease inhibitors, may reduce the metabolism of quazepam and increase the potential for benzodiazepine toxicity. A decrease in the quazepam dose may be needed. [28001] [28345] [32432]

Quetiapine: (Major) Avoid coadministration of lopinavir with quetiapine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Limited data, including some case reports, suggest that quetiapine may be associated with a significant prolongation of the QTc interval in rare instances. [28341] [29118] [33068] [33072] [33074] [65157] [65170] (Major) The manufacturer of quetiapine recommends a quetiapine dose reduction to one-sixth the original dose during concurrent administration of strong CYP3A4 inhibitors, such as ritonavir. When ritonavir is discontinued, the dose should be increased by 6-fold. The plasma concentrations of quetiapine may be elevated when administered concurrently with ritonavir. [29118] [47165]

Quinidine: (Major) Avoid coadministration of lopinavir with quinidine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Quinidine administration is associated with QT prolongation and torsade de pointes (TdP). [28341] [42280] [47357] [65157] [65170] (Major) Coadministration of HIV treatment doses of ritonavir and quinidine is contraindicated due to the potential for serious or life-threatening reactions, such as cardiac arrhythmias. Cautious consideration may be given to administering quinidine with boosting doses of ritonavir. Ritonavir is an inhibitor of CYP3A4 and increased plasma concentrations of drugs extensively metabolized by this enzyme, such as quinidine, should be expected with concurrent use. [28315] [42280] [46638] [47165] [47357]

Quinine: (Major) Avoid coadministration of lopinavir with quinine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Quinine has been associated with QT prolongation and rare cases of torsade de pointes (TdP). [28341] [31403] [65157] [65170] (Major) Concomitant use of quinine and ritonavir should be avoided due to increased quinine concentrations. In a study of healthy patients who received a single oral 600 mg dose of quinine with the 15th dose of ritonavir (200 mg PO Q12h for 9 days), there was a 4-fold increase in the mean quinine AUC and Cmax and an increase in the mean quinine elimination half-life (13.4 h vs. 11.2 h) when compared to quinine administered alone. There were no significant changes in the ritonavir pharmacokinetics. Ritonavir is a potent CYP3A4 inhibitor and quinine is a CYP3A4 substrate. [11191] [28315] [31403] [38968]

Rabeprazole: (Minor) Concurrent administration of rabeprazole with ritonavir may result in increased rabeprazole plasma concentrations; however, the clinical significance of this interaction is unclear. Rabeprazole is metabolized by the hepatic isoenzymes CYP2C19 and CYP3A4; ritonavir is a potent inhibitor of CYP3A4. Monitor for rabeprazole-associated adverse events if these drugs are administered together. [40337] [41276] [58664]

Ramelteon: (Moderate) The serum concentrations of ramelteon may increase when ramelteon is administered with strong CYP3A4 inhibitors like the anti-retroviral protease inhibitors. Because there is the potential for multiple CYP450 enzyme inhibition interactions between protease inhibitors and ramelteon, caution should be used if these 2 drugs are coadministered. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index. [31359] [31360] [4718] [5074] [8143] [8145]

Ranolazine: (Severe) Coadministration of lopinavir; ritonavir with ranolazine is contraindicated due to the potential for additive QT prolongation. Ranolazine is highly dependent on CYP3A for clearance and is associated with dose- and plasma concentration-related increases in the QTc interval. Lopinavir; ritonavir is a potent CYP3A inhibitor and is also associated with QT prolongation. [28341] [31938] (Severe) Concomitant use of ranolazine with ritonavir is contraindicated due to the potential for increased ranolazine plasma concentrations and therefore increased risk of QTc prolongation and possibly torsade de pointes. Ranolazine is a CYP3A4, CYP2D6, and P-glycoprotein (P-gp) substrate; ritonavir is a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6 and P-gp. Coadministration of another strong CYP3A4 inhibitor increased plasma concentrations of ranolazine by 220%. [31938] [47165]

Red Yeast Rice: (Severe) The risk of myopathy, including rhabdomyolysis, may be increased when anti-retroviral protease inhibitors are given in combination with most HMG-CoA reductase inhibitors. Since compounds in red yeast rice claim to have HMG-CoA reductase inhibitor activity, coadministration of red yeast rice with anti-retroviral protease inhibitors is not recommended. [5335] [5911]

Regorafenib: (Major) Avoid coadministration of regorafenib with ritonavir due to increased plasma concentrations of regorafenib and decreased plasma concentrations of the active metabolites M-2 and M-5, which may lead to increased toxicity. Regorafenib is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased regorafenib exposure by 33% and decreased exposure of M-2 and M-5 by 93% each. [47165] [51883]

Remifentanyl: (Moderate) Ritonavir is an inhibitor of the cytochrome P450 3A4 isoenzyme and may decrease the metabolism of remifentanyl if the two drugs are coadministered. [4718]

Repaglinide: (Moderate) Coadministration of repaglinide and protease inhibitors may increase or decrease glucose concentrations and increase repaglinide AUC; if coadministration is necessary, repaglinide dosage adjustment may be necessary and increased frequency of glucose monitoring are recommended. New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. In addition, repaglinide is a substrate of the hepatic isoenzyme CYP3A4 and the drug transporter organic anion transporting polypeptide OATP1B1; protease inhibitors are potent CYP3A4 inhibitors and inhibitors of OATP. [29751] [31281] [36049] [61511] [61513]

Retapamulin: (Moderate) Coadministration of retapamulin with strong CYP3A4 inhibitors, such as ritonavir, in patients younger than 24 months is not recommended. Systemic exposure of topically administered retapamulin may be higher in patients younger than 24 months than in patients 2 years and older. Retapamulin is a CYP3A4 substrate. [33239] [47165]

Revefenacin: (Major) Coadministration of revefenacin is not recommended with lopinavir because it could lead to an increase in systemic exposure of the active metabolite of revefenacin and an increased potential for anticholinergic adverse effects. The active metabolite of revefenacin is a substrate of OATP1B1 and OATP1B3; lopinavir is an inhibitor of OATP1B1. [28341] [56579] [61511] [61513] [63742]

Ribavirin: (Major) The concomitant use of ribavirin and anti-retroviral protease inhibitors should be done with caution as both can cause hepatic damage. Most protease inhibitors have been associated with episodes of liver toxicity, with lopinavir/low-dose ritonavir, fosamprenavir/low-dose ritonavir, and nelfinavir being less hepatotoxic and tipranavir/low-dose ritonavir being the most hepatotoxic. Hyperbilirubinemia is often associated with atazanavir and/or indinavir therapy but does not reflect liver damage and is related to the inhibition of UDP glucuronosyltransferase. Overall, the HCV-HIV International Panel recommends the management of hepatotoxicity should be based on the knowledge of the mechanisms involved for each drug. Furthermore, they state that there are lower rates of liver-related mortality in coinfecting patients taking HAART, even in those with end-stage liver disease, compared with patients not receiving HAART. Closely monitor patients for treatment-associated toxicities, especially hepatic decompensation. [34878]

Ribociclib: (Major) Avoid coadministration of lopinavir with ribociclib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Ribociclib has been shown to prolong the QT interval in a concentration-dependent manner. [28341] [61816] [65157] [65170] (Major) Avoid coadministration of ribociclib with ritonavir due to the potential for significantly increased exposure to ribociclib. If coadministration cannot be avoided, reduce the dose of ribociclib to 400 mg once daily. If ritonavir is discontinued, resume the previous ribociclib dose after at least 5 half-lives of ritonavir. Ribociclib is a CYP3A4 substrate. ritonavir is a strong CYP3A4 inhibitor. Coadministration with a strong inhibitor increased the ribociclib AUC and Cmax by 3.2-fold and 1.7-fold, respectively, in healthy volunteers. [61816]

Ribociclib; Letrozole: (Major) Avoid coadministration of lopinavir with ribociclib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Ribociclib has been shown to prolong the QT interval in a concentration-dependent manner. [28341] [61816] [65157] [65170] (Major) Avoid coadministration of ribociclib with ritonavir due to the potential for significantly increased exposure to ribociclib. If coadministration cannot be avoided, reduce the dose of ribociclib to 400 mg once daily. If ritonavir is discontinued, resume the previous ribociclib dose after at least 5 half-lives of ritonavir. Ribociclib is a CYP3A4 substrate. ritonavir is a strong CYP3A4 inhibitor. Coadministration with a strong inhibitor increased the ribociclib AUC and Cmax by 3.2-fold and 1.7-fold, respectively, in healthy volunteers. [61816]

Rifabutin: (Major) Coadministration of ritonavir and rifabutin results in clinically significant alterations of rifabutin pharmacokinetic parameters, with the rifabutin AUC being increased by 430%. In patients receiving any dosage of ritonavir, the dose of rifabutin should always be decreased to 150 mg every day or 300 mg three times per week. [46638] (Major) Coadministration with lopinavir; ritonavir (Kaletra) results in clinically significant alterations in rifabutin pharmacokinetics; the AUC increases by more than 300% and the metabolite, 25-O-des-acetyl-rifabutin, AUC increases by 47.5 fold. If these drugs are coadministered, the CDC recommends the adult dose of rifabutin be reduced to 150 mg every day or 300 mg three times per week. Increased monitoring for adverse reactions is warranted. [28341] [46638]

Rifampin: (Severe) Coadministration of rifampin and ritonavir results in markedly decreased ritonavir concentrations; HIV treatment failure and virologic resistance would be expected. Rifampin (300 or 600 mg daily for 10 days) decreases the AUC and Cmax of ritonavir (500 mg every 12 hours for 20 days) by 35% and 25%, respectively. Coadministration may lead to loss of virologic response if ritonavir is the sole protease inhibitor and increase the risk of hepatotoxicity. The DHHS/NIH HIV Treatment Guidelines recommend ritonavir and rifampin should not be coadministered and suggest the consideration of alternative antimycobacterial agents, such as rifabutin. However, CDC guidelines suggest no change in ritonavir or rifampin dose when the drugs are coadministered, but this appears to only be in the setting of low-dose ritonavir (i.e., 100 mg or 200 mg twice daily) used to 'boost' concentrations of other protease inhibitors. In this setting it would be less likely to produce adverse events than higher ritonavir doses; however, a net CYP3A4 induction still results when used with rifampin. [1299] [30314] [46638] (Severe) The coadministration of lopinavir; ritonavir and rifampin is contraindicated. Concurrent use may lead to loss of virologic response and possible resistance to lopinavir; ritonavir, the class of protease inhibitors, or other antiretroviral agents. [28341] [30314] [46638]

Rifapentine: (Major) Rifapentine is an inducer of CYP3A4 and CYP2C8/9, and should not be coadministered with protease inhibitors as complex interactions may lead to decreased plasma concentrations of the anti-retroviral agents. In one study, indinavir Cmax and AUC were reduced by 55% and 70%, respectively. The clearance of indinavir was increased 3-fold in the presence of rifapentine while half-life did not change. Additionally, HIV patients treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens; an alternative agent is recommended. [28483] [32432] [46638]

Rifaximin: (Moderate) Although the clinical significance of this interaction is unknown, concurrent use of rifaximin and lopinavir; ritonavir may substantially increase the systemic exposure to rifaximin; caution is advised if these drugs must be administered together. Rifaximin is a substrate for the drug transporters P-glycoprotein (P-gp) and organic anion transporting polypeptide (OATP); lopinavir is an inhibitor of OATP1B1 and ritonavir is a P-gp inhibitor. During one in vitro study, coadministration with cyclosporine, a potent P-gp

and OATP1B1 inhibitor, resulted in an 83-fold and 124-fold increase in the mean C_{max} and AUC of rifaximin, respectively. In patients with hepatic impairment, the effects of reduced metabolism and transporter inhibition may further increase exposure to rifaximin. [28341] [29289] [56579] [61510] [61511] [61513] (Moderate) Although the clinical significance of this interaction is unknown, concurrent use of rifaximin, a P-glycoprotein (P-gp) substrate, and ritonavir, a P-gp inhibitor, may substantially increase the systemic exposure to rifaximin; caution is advised if these drugs must be administered together. During one in vitro study, coadministration with cyclosporine, a potent P-gp inhibitor, resulted in an 83-fold and 124-fold increase in the mean C_{max} and AUC of rifaximin, respectively. In patients with hepatic impairment, the effects of reduced metabolism and P-gp inhibition may further increase exposure to rifaximin. [28341] [28380] [29289] [56579]

Rilpivirine: (Major) Avoid coadministration of lopinavir with rilpivirine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Supratherapeutic doses of rilpivirine (75 to 300 mg/day) have caused QT prolongation. [28341] [44376] [65157] [65170]

Riluzole: (Moderate) Coadministration of riluzole with ritonavir may result in decreased riluzole efficacy. In vitro findings suggest decreased riluzole exposure is likely. Riluzole is a CYP1A2 substrate and ritonavir is a CYP1A2 inducer. [29747] [47165]

Rimegepant: (Major) Avoid coadministration of rimegepant with ritonavir; concurrent use may significantly increase rimegepant exposure. Rimegepant is a CYP3A4 and P-gp substrate; ritonavir is a strong CYP3A4 inhibitor and P-gp inhibitor. Coadministration of rimegepant with another strong CYP3A4 inhibitor increased rimegepant exposure by 4-fold. [28380] [34557] [47165] [65052]

Riociguat: (Major) Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-glycoprotein (P-gp)/breast cancer resistance protein (BCRP) inhibitors, such as ritonavir, increases riociguat exposure and may result in hypotension. Consider a starting adult dose of 0.5 mg PO three times a day when initiating riociguat in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat. [56096]

Risperidone: (Major) Avoid coadministration of lopinavir with risperidone due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes (TdP), primarily in the overdose setting. [28225] [28341] [28414] [65157] [65170] (Moderate) Ritonavir may increase risperidone exposure; use together with caution and monitor for adverse effects of risperidone, including QT prolongation or other risperidone side effects. A decreased dosage of risperidone may be required. Risperidone is primarily metabolized by CYP2D6 and is also partially metabolized by CYP3A4; ritonavir inhibits both CYP2D6 and CYP3A4. [22256] [28414] [47165] [59321] [63411]

Rivaroxaban: (Major) Avoid concomitant administration of rivaroxaban and ritonavir; significant increases in rivaroxaban exposure may increase bleeding risk. Rivaroxaban is a substrate of CYP3A4/5 and the P-glycoprotein (P-gp) transporter. Concurrent use of a single dose of rivaroxaban and ritonavir, a combined P-gp and strong CYP3A4 inhibitor, led to an increase in the rivaroxaban AUC by 150% and C_{max} by 60%. Similar increases in pharmacodynamic effects such as factor Xa inhibition and PT prolongation were also observed. [28315] [44854] [47165]

Rocuronium: (Moderate) Use caution if ritonavir is coadministered with rocuronium due to the potential for increased rocuronium exposure which may increase the risk of toxicity. Limited data suggests that rocuronium is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. [47165] [65210] [65228] [65229]

Roflumilast: (Major) Patients receiving roflumilast may have altered serum concentrations if coadministered with ritonavir. Ritonavir is a potent inhibitor and an inducer of CYP3A4, and roflumilast is a CYP3A4 substrate. Specific pharmacokinetic study of this potential interaction has not been conducted. [11416] [43551] [5044] [5110]

Romidepsin: (Major) Avoid coadministration of lopinavir with romidepsin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Romidepsin has also been reported to prolong the QT interval. [28341] [37292] [65157] [65170] (Moderate) Monitor for toxicity related to increased romidepsin exposure and follow the dose modifications for toxicity during initial administration of romidepsin with ritonavir. Romidepsin is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. In a pharmacokinetic drug interaction trial a strong CYP3A4 inhibitor increased romidepsin AUC by approximately 25%. [37292] [47165]

Rosuvastatin: (Major) Due to CYP3A4 inhibition by ritonavir, the risk of myopathy (including rhabdomyolysis) may be increased when ritonavir is given in combination with rosuvastatin. If coadministration is necessary, use the lowest possible dose of rosuvastatin. Alternatively, consider using pravastatin or fluvastatin; however, fluvastatin is partially metabolized (about 20%) by CYP3A4 and is generally recommended to be used cautiously with protease inhibitors. [46638] [5044] [5045] (Major) When rosuvastatin was coadministered with lopinavir; ritonavir in healthy volunteers, the C_{max} and AUC of rosuvastatin was increased 5-fold and 2-fold, respectively. When possible, concurrent use of rosuvastatin and lopinavir; ritonavir should be avoided. If rosuvastatin must be used concurrently with lopinavir; ritonavir, limit the rosuvastatin adult dosage to 10 mg/day. Rosuvastatin is a substrate of the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is OATP1B1 inhibitor. [28341] [56579] [61510] [61511] [61513]

Ruxolitinib: (Major) Reduce the ruxolitinib dosage during coadministration with ritonavir in patients with myelofibrosis (MF) or polycythemia vera (PV) as increased ruxolitinib exposure and toxicity may occur; no dose adjustments are necessary for patients with graft-versus-host disease. In MF patients, reduce the initial dose to 10 mg PO twice daily for platelet count of 100,000 cells/mm³ or more and 5 mg PO once daily for platelet count of 50,000 to 99,999 cells/mm³. In PV patients, reduce the initial dose to 5 mg PO twice daily. Avoid the use of ritonavir in MF or PV patients who are stable on a ruxolitinib dose of 5 mg PO once daily. In MF or PV patients stable on ruxolitinib dose of 10 mg PO twice daily or more, reduce dose by 50%; in patients stable on ruxolitinib dose of 5 mg PO twice daily, reduce ruxolitinib to 5 mg PO once daily. Additional dose modifications should be made with frequent monitoring of safety and efficacy. Ruxolitinib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. [46782] [47165]

Sacubitril; Valsartan: (Moderate) Concurrent use of lopinavir with valsartan may result in elevated valsartan serum concentrations. Valsartan is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. Monitor for increased toxicities if these drugs are given together. [56575] [61510] [61511] [61513] (Minor) Valsartan is a substrate of the hepatic efflux transporter MRP2 and ritonavir is an inhibitor of MRP2. Coadministration may increase systemic exposure to valsartan. Patients should be monitored for adverse effects of valsartan during coadministration. [28315] [29130] [36646] [39870] [60860]

Salmeterol: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28318] [28341] [32901] [33925] [41231] [65157] [65170] (Major) Avoid coadministration of salmeterol with ritonavir. The coadministration of salmeterol with CYP3A4 inhibitors can result in elevated salmeterol plasma concentrations and increased risk for adverse reactions, particularly cardiovascular effects. [28315] [28467] [47165]

Sapropterin: (Moderate) Caution is advised with the concomitant use of sapropterin and ritonavir as coadministration may result in increased systemic exposure of ritonavir. Ritonavir is a substrate for the drug transporter P-glycoprotein (P-gp); in vitro data show that sapropterin may inhibit P-gp. If these drugs are used together, closely monitor for increased side effects of ritonavir. [28315] [33635]

Saquinavir: (Major) Avoid coadministration of lopinavir; ritonavir with saquinavir due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. When coadministered with lopinavir; ritonavir 400/100 mg twice daily, the saquinavir dose is 1,000 mg twice daily. Lopinavir; ritonavir is associated with QT prolongation. Saquinavir boosted with ritonavir increases the QT interval in a dose-dependent fashion, which may increase the risk for serious arrhythmias such as torsade de pointes (TdP). [28341] [28995] [65157] [65170]

Saxagliptin: (Major) The metabolism of saxagliptin is primarily mediated by CYP3A4/5. The saxagliptin dose is limited to 2.5 mg once daily when coadministered with a strong CYP 3A4/5 inhibitor such as the ritonavir component of lopinavir; ritonavir. In addition, new onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [28341] [30575] [36111] (Major) The metabolism of saxagliptin is primarily mediated by CYP3A4/5. The saxagliptin dose is limited to 2.5 mg once daily when coadministered with a strong CYP3A4/5 inhibitor such as ritonavir. New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have also been reported with use of anti-retroviral protease inhibitors, such as ritonavir. Patients on antidiabetic therapy should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [36111] [7238] [7335]

Secobarbital: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [28341] [46638] (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [46638]

Segesterone Acetate; Ethinyl Estradiol: (Major) Coadministration may result in an increased or decreased effect of segesterone. Contraceptive efficacy may be reduced. Segesterone is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor and CYP3A4 inducer. [47165] [63429] (Major) Ritonavir increases the metabolism of oral contraceptives and non-oral combination contraceptives; coadministration decreases ethinyl estradiol AUC by 40% and Cmax by 32%. Women receiving hormonal contraceptives and anti-retroviral protease inhibitors (PIs), such as ritonavir, should be instructed to report any breakthrough bleeding or other adverse effects to their prescribers. It may be prudent for women who receive hormonal contraceptives concurrently with PIs to use an additional method of contraception to protect against unwanted pregnancy. Additionally, because hormonal contraceptives do not protect against the transmission of HIV/AIDS and other sexually transmitted diseases, women who receive hormonal contraceptives concurrently with PIs should use an additional barrier method of contraception such as condoms. [46638] [5044]

Selegiline: (Moderate) Concurrent administration of selegiline with ritonavir may result in elevated selegiline plasma concentrations. Selegiline is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is a potent inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [47165] [58664] [8837]

Selexipag: (Moderate) Concurrent use of lopinavir with selexipag may result in elevated selexipag serum concentrations. Selexipag is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. Monitor for increased toxicities if these drugs are given together. [60472] [61510] [61511] [61513]

Selumetinib: (Major) Avoid coadministration of selumetinib and ritonavir due to the risk of increased selumetinib exposure which may increase the risk of adverse reactions. If coadministration is unavoidable, reduce the dose of selumetinib to 20 mg/m² PO twice daily if original dose was 25 mg/m² twice daily and 15 mg/m² PO twice daily if original dose was 20 mg/m² twice daily. If ritonavir is discontinued, resume the original selumetinib dose after 3 elimination half-lives of ritonavir. Selumetinib is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased selumetinib exposure by 49%. [47165] [65246]

Sertraline: (Major) Avoid coadministration of lopinavir with sertraline due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. The risk of sertraline-induced QT prolongation is generally considered to be low in clinical practice. Its effect on QTc interval is minimal (typically less than 5 msec), and the drug has been used safely in patients with cardiac disease (e.g., recent myocardial infarction, unstable angina, chronic heart failure). [28341] [28343] [64391] [64392] [64394] [64395] [64396] [65157] [65170]

Short-acting beta-agonists: (Major) Avoid coadministration of lopinavir with short-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28341] [33925] [65157] [65170]

Sibutramine: (Moderate) Due to ritonavir's potential inhibitory effects on various hepatic isoenzymes, close monitoring of serum drug concentrations and/or therapeutic and adverse effects is required when sibutramine is coadministered with ritonavir; dosage reduction may be needed. [4718]

Sildenafil: (Major) Coadministration of ritonavir is contraindicated in patients receiving sildenafil for pulmonary arterial hypertension (PAH). If used for erectile dysfunction, the dose of sildenafil should not exceed 25 mg in 48 hours with increased monitoring for adverse reactions during times of coadministration. Concurrent use substantially increases the sildenafil plasma concentrations and may result in increased associated adverse events including hypotension, syncope, visual changes, and prolonged erection. Ritonavir, a strong CYP3A4 inhibitor, increased the AUC of sildenafil, a sensitive CYP3A4 substrate, by 11-fold in a drug interaction study. [2548] [28315] [46638]

Silodosin: (Severe) Concurrent use of silodosin and ritonavir is contraindicated. Silodosin is extensively metabolized by CYP3A4; ritonavir is a potent inhibitor of this enzyme. Also of note, silodosin is a P-glycoprotein (P-gp) substrate and ritonavir is a P-gp inhibitor. Coadministration may cause significant increases in silodosin plasma concentrations, potentially resulting in adverse events. [34483]

Simeprevir: (Major) Avoid concurrent use of simeprevir and lopinavir; ritonavir. Inhibition of CYP3A4, organic anion transporting polypeptide (OATP1B1), and P-glycoprotein (P-gp) by lopinavir; ritonavir may increase the plasma concentrations of simeprevir, resulting in adverse effects. [28341] [28380] [56471] [56579] [61510] [61511] [61513] (Major) Avoid concurrent use of simeprevir and ritonavir. Inhibition of CYP3A4 and P-glycoprotein (P-gp) by ritonavir causes significantly increased plasma concentrations of simeprevir, potentially resulting in adverse effects. [28380] [47165] [56471] [56579]

Simvastatin: (Severe) The coadministration of anti-retroviral protease inhibitors with simvastatin is contraindicated. Taking these drugs together may significantly increase the serum concentration of simvastatin; thereby increasing the risk of myopathy and rhabdomyolysis. One report has demonstrated that ritonavir plus saquinavir therapy markedly increases the AUC for simvastatin by 3059%. Simvastatin is a substrate for CYP3A4 and the drug transporter organic anion transporting polypeptide (OATP1B1); protease inhibitors are CYP3A4 and OATP inhibitors. [28605] [39682] [46638] [61510] [61511] [61512] [61513]

Simvastatin; Sitagliptin: (Severe) The coadministration of anti-retroviral protease inhibitors with simvastatin is contraindicated. Taking these drugs together may significantly increase the serum concentration of simvastatin; thereby increasing the risk of myopathy and rhabdomyolysis. One report has demonstrated that ritonavir plus saquinavir therapy markedly increases the AUC for simvastatin by 3059%. Simvastatin is a substrate for CYP3A4 and the drug transporter organic anion transporting polypeptide (OATP1B1); protease inhibitors are CYP3A4 and OATP inhibitors. [28605] [39682] [46638] [61510] [61511] [61512] [61513] (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic agents should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30575]

Siponimod: (Major) Avoid coadministration of lopinavir with siponimod due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Consult a cardiologist. Siponimod therapy prolonged the QT interval at recommended doses in a clinical study. Lopinavir is associated with QT prolongation. [28341] [64031] [65157] [65170] (Moderate) Concomitant use of siponimod and ritonavir may increase siponimod exposure. If the patient is also receiving a drug regimen containing a moderate CYP2C9 inhibitor, use of siponimod is not recommended due to a significant increase in siponimod exposure. Siponimod is a CYP2C9 and CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration with a moderate CYP2C9/CYP3A4 dual inhibitor led to a 2-fold increase in the exposure of siponimod. [47165] [64031]

Sirolimus: (Major) Avoid the use of sirolimus with potent CYP3A4 inhibitors, such as protease inhibitors. Protease inhibitors may affect absorption and elimination of sirolimus leading to increased blood concentrations. Sirolimus is extensively metabolized by CYP3A4 in the gut and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen by the P-glycoprotein drug efflux pump. Sirolimus is potentially recycled between enterocytes and the gut lumen to allow continued metabolism by CYP3A4. [28610] [28995] [47165]

Sitagliptin: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Another possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients taking antidiabetic agents should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [30575]

Sodium Bicarbonate: (Moderate) Concurrent administration of tipranavir and ritonavir with antacids results in decreased tipranavir concentrations. Administer tipranavir and ritonavir 2 hours before or 1 hour after antacids. [1800] [1802]

Sodium Oxybate: (Major) One case report describes a possible interaction between sodium oxybate and ritonavir and saquinavir, leading to repetitive, clonic contractions. The patient also experienced shallow respirations, a heart rate of 40 beats per min, and was responsive only to painful stimuli. The exact contribution of ritonavir and saquinavir to this reaction cannot be determined since several other compounds were detected through a urinary toxin screen. [2546]

Sofosbuvir; Velpatasvir; Voxilaprevir: (Major) Avoid concurrent administration of voxilaprevir and lopinavir. Taking these medications together may increase voxilaprevir plasma concentrations, potentially increasing the risk for adverse events. Voxilaprevir is a substrate for the drug transporter Organic Anion Transporting Polypeptides 1B1 (OATP1B1). Lopinavir is an OATP1B1 inhibitor. [61510] [61511] [61513] [62131]

Solifenacin: (Major) Avoid coadministration of lopinavir with solifenacin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Solifenacin has been associated with dose-dependent prolongation of the QT interval. Torsade de pointes (TdP) has been reported with postmarketing use, although causality was not determined. [28341] [30515] [65157] [65170] (Moderate) Do not exceed a 5 mg daily dose of solifenacin if coadministered with ritonavir. The plasma concentrations of solifenacin may be elevated when administered concurrently with ritonavir. Ritonavir is a strong CYP3A4 inhibitor, while solifenacin is a CYP3A4 substrate. Coadministration of another strong CYP3A4 inhibitor increased the mean Cmax and AUC of solifenacin increased by 1.5 and 2.7-fold, respectively. [30515] [47165]

Somatropin, rh-GH: (Minor) When somatropin, an inducer of CYP3A4, and anti-retroviral protease inhibitors, a CYP3A4 substrate, are coadministered, patients should be monitored for changes in anti-retroviral efficacy. Published data indicate that in HIV-infected patients receiving somatropin for wasting or HIV-associated adipose redistribution syndrome (HARS), somatropin did not adversely affect antiretroviral effectiveness as indicated by no change in the concentration of circulating CD4 counts or viral load. [10378]

Sonidegib: (Major) Avoid the concomitant use of sonidegib and ritonavir as sonidegib levels may be significantly increased resulting in an increased risk of adverse events, particularly musculoskeletal toxicity. Sonidegib is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Coadministration of a strong CYP3A4 inhibitor increased the mean Cmax and AUC of sonidegib by 2.2-fold and 1.5-fold, respectively [28315] [58864] [60000] [60002]

Sorafenib: (Major) Avoid coadministration of lopinavir with sorafenib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Interrupt or discontinue sorafenib if QT prolongation occurs. Both drugs have been associated with QT prolongation. [28341] [31832] [65157] [65170]

Sotalol: (Major) Avoid coadministration of lopinavir with sotalol due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Sotalol administration is associated with QT prolongation and torsade de pointes (TdP). Proarrhythmic events should be anticipated after initiation of therapy and after each upward dosage adjustment. [28234] [28341] [65157] [65170] (Major) The use of ritonavir could result in QT prolongation. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with ritonavir include sotalol. [28234] [47165]

St. John's Wort, Hypericum perforatum: (Severe) Use of St. John's wort with protease inhibitors is contraindicated. St. John's wort is an inducer of CYP3A and is expected to significantly decrease the plasma concentrations of all currently marketed protease inhibitors. Reductions in plasma concentrations of these drugs could lead to HIV treatment failures or the development of viral-resistance. St. John's wort in all forms, including teas, should be avoided in HIV patients treated with these agents. [2718] [28315] [28731] [28995] [46638] [4718] [4865] [4935] [8102]

Sufentanil: (Moderate) Because the dose of the sufentanil sublingual tablets cannot be titrated, consider an alternate opiate if a protease inhibitor must be administered. Consider a reduced dose of sufentanil injection with frequent monitoring for respiratory depression and sedation if concurrent use of a protease inhibitor is necessary. If a protease inhibitor is discontinued, consider increasing the sufentanil injection dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Sufentanil is a CYP3A4 substrate, and coadministration with a strong CYP3A4 inhibitor like protease inhibitors can increase sufentanil exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of sufentanil. If a protease inhibitor is discontinued, sufentanil plasma concentrations will decrease resulting in reduced efficacy of the opioid and potential withdrawal syndrome in a patient who has developed physical dependence to sufentanil. [30966] [47165] [63731]

Sulfonylureas: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. A possible mechanism is impairment of beta-cell function. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic agents should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. [28380] [29012] [30575] [31320] [34471] [34472] [34489] [34490] [34491] [34557] [47165] [51227] [58000] [58763]

Sunitinib: (Major) Avoid coadministration of lopinavir with sunitinib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs are associated with QT prolongation. [28341] [31970] [65157] [65170] (Major) Avoid coadministration of ritonavir with sunitinib if possible due to increased sunitinib exposure, which may increase the risk of QT prolongation. If concomitant use is unavoidable, consider reducing the dose of sunitinib in 12.5 mg decrements based on individual safety and tolerability to a minimum of 37.5 mg (GIST and RCC) or 25 mg (pNET) daily. In the adjuvant RCC study, the minimum dose administered was 37.5 mg. Sunitinib is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased exposure to sunitinib and its primary active metabolite by 51%. [31970] [47165]

Suvorexant: (Major) Coadministration of suvorexant and ritonavir is not recommended due to the potential for significantly increased suvorexant exposure. Suvorexant is a CYP3A4 substrate. Ritonavir is a strong CYP3A4 inhibitor. Coadministration of another strong CYP3A4 inhibitor increased the suvorexant AUC by 2.8-fold. [57780]

Tacrolimus: (Major) Avoid coadministration of lopinavir with tacrolimus due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Tacrolimus may prolong the QT interval and cause torsade de pointes (TdP). [28341] [28611] [55401] [60497] [65157] [65170] (Moderate) A reduced dose of tacrolimus based on tacrolimus whole blood concentrations is recommended if coadministered with ritonavir. Concurrent administration is expected to increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions including neurotoxicity and QT prolongation. Tacrolimus is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. [28611] [47165]

Tadalafil: (Major) For the treatment of erectile dysfunction, do not exceed 10 mg of tadalafil within 72 hours of ritonavir for the 'as needed' dose or 2.5 mg daily for the 'once-daily' dose. Avoid the use of tadalafil for pulmonary hypertension during the initiation of ritonavir therapy. Stop tadalafil at least 24 hours prior to starting ritonavir. After at least 1 week of ritonavir therapy, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based on tolerability. Coadministration of ritonavir with tadalafil results in a 124% increase in tadalafil AUC. Substantially increased tadalafil plasma concentrations may result in increased adverse events including hypotension, syncope, visual changes, and prolonged erection. It should be noted that during once daily administration of tadalafil, the presence of continuous plasma tadalafil concentrations may change the potential for interactions with potent inhibitors of CYP3A4. [28220] [28315] [40259]

Talazoparib: (Moderate) Monitor for an increase in talazoparib-related adverse reactions if coadministration with ritonavir is necessary. Talazoparib is a P-glycoprotein (P-gp) substrate and ritonavir is a P-gp inhibitor. Coadministration with other P-gp inhibitors increased talazoparib exposure by 8% to 45%. [28380] [34557] [63651]

Tamoxifen: (Major) Avoid coadministration of lopinavir with tamoxifen due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Tamoxifen has been reported to prolong the QT interval, usually in overdose or when used in high doses. Rare case reports of QT prolongation have also been described when tamoxifen is used at lower doses. [28341] [61870] [61871] [61872] [63589] [65157] [65170]

Tamsulosin: (Major) Plasma concentrations of tamsulosin may be increased with concomitant use of anti-retroviral protease inhibitors. Tamsulosin is extensively metabolized by CYP3A4 and CYP2D6 hepatic enzymes. In clinical evaluation, concomitant treatment with a strong CYP3A4 inhibitor resulted in significant increases in tamsulosin exposure. Such increases in tamsulosin concentrations may be expected to produce clinically significant and potentially serious side effects, such as hypotension. Therefore, concomitant use of tamsulosin with a strong CYP3A4 inhibitor, or an agent with both CYP3A4 and CYP2D6 inhibitor activity, should be avoided. [29677] [4194] [8102]

Tasimelteon: (Major) Concurrent use of tasimelteon and strong inhibitors of CYP3A4, such as ritonavir, should be avoided if possible. Because tasimelteon is partially metabolized via CYP3A4, a large increase in exposure of tasimelteon with the potential for adverse reactions is possible if these drugs are coadministered. During administration of tasimelteon and another potent CYP3A4 inhibitor, tasimelteon exposure increased by about 50%. [56665]

Tazemetostat: (Major) Avoid coadministration of tazemetostat with ritonavir as concurrent use may increase tazemetostat exposure and the frequency and severity of adverse reactions. Tazemetostat is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Coadministration of a moderate CYP3A4 inhibitor increased tazemetostat exposure by 3.1-fold. [47165] [64952]

Telaprevir: (Major) Concurrent administration of lopinavir; ritonavir with telaprevir is not recommended. If lopinavir; ritonavir and telaprevir are coadministered, monitor the patient closely for HIV and hepatitis C treatment failures. [44393] [5070]

Telavancin: (Major) Avoid coadministration of lopinavir with telavancin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [28341] [36615] [65157] [65170]

Telithromycin: (Major) Avoid coadministration of lopinavir with telithromycin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Telithromycin is associated with QT prolongation and torsade de pointes (TdP). [28156] [28341] [65157] [65170] (Major) Avoid coadministration of telithromycin and ritonavir due to increased telithromycin exposure which may increase the risk of QT prolongation; ritonavir exposure may also increase. Both drugs are substrates and strong inhibitors of CYP3A4. [28156] [47165]

Telotristat Ethyl: (Moderate) Use caution if coadministration of telotristat ethyl and lopinavir is necessary, as the systemic exposure of lopinavir may be decreased resulting in reduced efficacy and viral resistance; exposure to telotristat ethyl may also be increased. If these drugs are used together, monitor patients for suboptimal efficacy of lopinavir as well as an increase in adverse reactions related to telotristat ethyl. Lopinavir is a CYP3A4 substrate. The mean C_{max} and AUC of another sensitive CYP3A4 substrate was decreased by 25% and 48%, respectively, when co-administered with telotristat ethyl; the mechanism of this interaction appears to be that telotristat ethyl increases the glucuronidation of the CYP3A4 substrate. Additionally, the active metabolite of telotristat ethyl, telotristat, is a substrate of P-glycoprotein (P-gp) and lopinavir is a P-gp inhibitor. Exposure to telotristat ethyl may increase. [28341] [56579] [61795] (Moderate) Use caution if coadministration of telotristat ethyl and ritonavir is necessary, as the systemic exposure of ritonavir may be decreased resulting in reduced efficacy; exposure to telotristat ethyl may also be increased. If these drugs are used together, monitor patients for suboptimal efficacy of ritonavir as well as an increase in adverse reactions related to telotristat ethyl. Ritonavir is a CYP3A4 substrate. The mean C_{max} and AUC of another sensitive CYP3A4 substrate was decreased by 25% and 48%, respectively, when coadministered with telotristat ethyl; the mechanism of this interaction appears to be that telotristat ethyl increases the glucuronidation of the CYP3A4 substrate. Coadministration with a strong CYP3A4 inducer decreased the ritonavir AUC and C_{max} by 35% and 25%,

respectively. Additionally, the active metabolite of telotristat ethyl, telotristat, is a substrate of P-glycoprotein (P-gp) and ritonavir is a P-gp inhibitor. Exposure to telotristat ethyl may increase. [28380] [34557] [61795]

Temsirolimus: (Major) Avoid coadministration of ritonavir with temsirolimus due to increased plasma concentrations of the primary active metabolite of temsirolimus (sirolimus); exposure to ritonavir may also increase. If concomitant use is unavoidable, consider reducing the dose of temsirolimus to 12.5 mg per week. Allow a washout period of approximately 1 week after discontinuation of ritonavir before increasing temsirolimus to its original dose. Temsirolimus is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor did not significantly affect temsirolimus exposure, but increased the AUC and C_{max} of sirolimus by 3.1-fold and 2.2-fold, respectively. Ritonavir is also a P-glycoprotein (P-gp) substrate and temsirolimus is a P-gp inhibitor. Concomitant use may lead to increased concentrations of ritonavir. [34557] [47165] [50586]

Teniposide: (Moderate) Concurrent administration of teniposide with ritonavir may result in elevated teniposide plasma concentrations. Teniposide is a substrate for CYP3A4 and P-glycoprotein (P-gp); ritonavir inhibits both CYP3A4 and P-gp. Caution and close monitoring are advised if these drugs are administered together. [28498] [34660] [47165] [48961] [58664]

Tenofovir Alafenamide: (Moderate) Concurrent use of lopinavir with tenofovir alafenamide may result in elevated tenofovir serum concentrations. Tenofovir alafenamide is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. When 10 mg of tenofovir alafenamide was administered daily with lopinavir; ritonavir (800 mg/200 mg PO daily), the tenofovir C_{max} and AUC increased by 2.19-fold and 1.47-fold, respectively. Monitor for increased toxicities if these drugs are given together. [60269] [61510] [61511] [61513]

Tenofovir Alafenamide: (Moderate) Concurrent use of lopinavir with tenofovir alafenamide may result in elevated tenofovir serum concentrations. Tenofovir alafenamide is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. When 10 mg of tenofovir alafenamide was administered daily with lopinavir; ritonavir (800 mg/200 mg PO daily), the tenofovir C_{max} and AUC increased by 2.19-fold and 1.47-fold, respectively. Monitor for increased toxicities if these drugs are given together. [60269] [61510] [61511] [61513]

Tenofovir, PMPA: (Moderate) Caution is advised when administering tenofovir, PMPA, a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate, concurrently with inhibitors of P-gp and BCRP, such as ritonavir. Coadministration may result in increased absorption of tenofovir. Monitor for tenofovir-associated adverse reactions. [28193] [58664] (Minor) There are varying results in reports of an interaction between tenofovir and lopinavir; ritonavir. In one report, the concurrent administration of tenofovir with lopinavir; ritonavir increased tenofovir C_{max} 31%, AUC 34%, and C_{min} 29%, with slight (15%) decreases in lopinavir C_{max} and AUC; the alterations may be a food effect rather than a drug-drug interaction. In another report, lopinavir; ritonavir (400 mg; 100 mg PO twice daily for 14 days) increased the tenofovir (300 mg/day PO) C_{min} 51% and AUC 32%, with no effect seen on lopinavir; ritonavir pharmacokinetics. While the clinical significance of this interaction is unknown, and is suspected to be insignificant, patients receiving lopinavir; ritonavir with tenofovir should be monitored for tenofovir-associated adverse events. [46638]

Terbinafine: (Moderate) Caution is advised when administering terbinafine with ritonavir. Although this interaction has not been studied by the manufacturer, and published literature suggests the potential for interactions to be low, taking these drugs together may alter the systemic exposure of terbinafine. Predictions about the interaction can be made based on the metabolic pathways of both drugs. Terbinafine is metabolized by at least 7 CYP isoenzymes, with major contributions coming from CYP1A2, CYP2C9, and CYP3A4; ritonavir is an inducer of CYP1A2 and CYP2C9, and an inhibitor/inducer of CYP3A4. Monitor patients for adverse reactions and breakthrough fungal infections if these drugs are coadministered. [37590] [43880] [43881] [47165] [56538]

Terbutaline: (Major) Avoid coadministration of lopinavir with short-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28341] [33925] [65157] [65170]

Terfenadine: (Severe) Caution should be used in patients receiving protease inhibitors concurrently with drugs metabolized via CYP3A4 and known to cause QT prolongation. Protease inhibitors inhibit the CYP3A4 isoenzyme at clinically relevant concentrations, which may lead to increased serum concentrations of terfenadine and an increased potential for QT prolongation or other adverse effects. Serious and/or life-threatening drug interactions could potentially occur between protease inhibitors and terfenadine. [141] [1800] [4865] [5044]

Tesamorelin: (Minor) Use caution when coadministering tesamorelin with ritonavir as their concurrent use may alter ritonavir plasma concentrations. In a pharmacokinetic study, multiple 2 mg doses of tesamorelin administered with ritonavir resulted in a 9% decrease in ritonavir AUC and an 11% decrease in ritonavir C_{max}. The clinical impact of these pharmacokinetic changes is unknown; however, patients should be monitored for decreased ritonavir efficacy. [42405]

Testosterone: (Moderate) Concurrent administration of testosterone with ritonavir may result in elevated plasma concentrations of testosterone and ritonavir. Testosterone is a substrate of the hepatic isoenzyme CYP3A4 and the drug transporter P-glycoprotein (P-gp). Ritonavir is a CYP3A4 and P-gp inhibitor. In addition, testosterone inhibits P-gp; ritonavir is a substrate of P-gp. Caution and close monitoring are advised if these drugs are administered together. [11580] [11581] [28380] [56579]

Tetrabenazine: (Major) Avoid coadministration of lopinavir with tetrabenazine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Tetrabenazine causes a small increase in the corrected QT interval (QTc). [28341] [34389] [65157] [65170]

Tezacaftor, Ivacaftor: (Major) If ritonavir and ivacaftor are taken together, administer ivacaftor at the usual recommended dose but reduce the frequency to twice weekly. Ivacaftor is a CYP3A substrate and ritonavir is a CYP3A inhibitor. Coadministration with another strong CYP3A inhibitor increased ivacaftor exposure by 8.5-fold. [48524] (Major) Reduce the dosing frequency of tezacaftor; ivacaftor when coadministered with ritonavir; coadministration may increase tezacaftor; ivacaftor exposure and adverse reactions. When combined, dose

1 tezacaftor; ivacaftor combination tablet twice a week, approximately 3 to 4 days apart (i.e., Day 1 and Day 4). The evening dose of ivacaftor should not be taken. Both tezacaftor and ivacaftor are CYP3A substrates (ivacaftor is a sensitive substrate); ritonavir is a strong CYP3A inhibitor. Coadministration of a strong CYP3A inhibitor increased tezacaftor and ivacaftor exposure 4- and 15.6-fold, respectively. [47165] [62870]

Theophylline, Aminophylline: (Moderate) Ritonavir decreased theophylline AUC and Cmax by 43% and 52%, respectively, when the two drugs were coadministered. Higher dosages of aminophylline might be required. [1800] [5044] (Moderate) Ritonavir decreased theophylline AUC and Cmax by 43% and 52%, respectively, when the two drugs were coadministered. If these drugs are used together, therapeutic drug monitoring should be considered. Higher dosages of theophylline might be required. [47165]

Thiazolidinediones: (Moderate) New onset diabetes mellitus, exacerbation of diabetes mellitus, and hyperglycemia due to insulin resistance have been reported with use of anti-retroviral protease inhibitors. Onset averaged approximately 63 days after initiating protease inhibitor therapy, but has occurred as early as 4 days after beginning therapy. Diabetic ketoacidosis has occurred in some patients including patients who were not diabetic prior to protease inhibitor treatment. Patients on antidiabetic agents should be closely monitored for changes in glycemic control, specifically hyperglycemia, if protease inhibitor therapy is initiated. In addition, coadministration of atazanavir with rosiglitazone may result in elevated rosiglitazone plasma concentrations. Rosiglitazone is a substrate for CYP2C8; atazanavir is a weak inhibitor of CYP2C8. [28142] [28172] [28380] [30575] [31320] [34557] [47165] [50768] [51227]

Thiopental: (Major) Barbiturates may increase the metabolism of lopinavir and lead to decreased antiretroviral efficacy. In addition, coadministration of lopinavir boosted with ritonavir may induce the CYP metabolism of barbiturates, resulting in decreased barbiturate concentrations. Appropriate dose adjustments necessary to ensure optimum levels of both anti-retroviral agent and the barbiturate are unknown; however, once daily lopinavir; ritonavir should not be used. Anticonvulsant serum concentrations should be monitored closely if these agents are added; the patient should be observed for changes in the clinical efficacy of the antiretroviral or anticonvulsant regimen. [28341] [46638] (Major) Concurrent use of ritonavir with phenobarbital or other barbiturates should be done cautiously. Increased doses of anticonvulsants may be required due to metabolism induction by ritonavir. However, since these anticonvulsants are hepatic enzyme inducing drugs, increased metabolism of protease inhibitors may occur, leading to decreased antiretroviral efficacy. Close monitoring of drug concentrations and/or therapeutic and adverse effects is required. [46638]

Thioridazine: (Severe) Coadministration of lopinavir with thioridazine is contraindicated due to the potential for additive QT prolongation. Thioridazine is associated with a well-established risk of QT prolongation and torsades de pointes (TdP). Lopinavir is associated with QT prolongation. [28225] [28293] [28341] (Moderate) Close clinical monitoring is recommended during coadministration; thioridazine dose reductions may be required. The plasma concentrations of thioridazine may be elevated when administered concurrently with ritonavir. Elevated levels of thioridazine may result in prolongation of the QTc interval and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsades de pointes. [43069] [47165]

Thiotepea: (Major) Avoid the concomitant use of thiotepea and ritonavir if possible; reduced metabolism to the active thiotepea metabolite may result in decreased thiotepea efficacy. Consider an alternative agent with no or minimal potential to inhibit CYP3A4. If coadministration is necessary, monitor patients for signs of reduced thiotepea efficacy. In vitro, thiotepea is metabolized via CYP3A4 to the active metabolite, TEPA; ritonavir is a strong CYP3A4 inhibitor. [47165] [61718]

Tiagabine: (Moderate) Concurrent administration of tiagabine with ritonavir may result in elevated tiagabine plasma concentrations. Tiagabine is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [58664] [7573]

Ticagrelor: (Major) Avoid the concomitant use of ticagrelor and ritonavir. Ticagrelor is a substrate of CYP3A4/5 and P-glycoprotein (P-gp), and ritonavir is a potent CYP3A4 inhibitor and a P-gp inhibitor. Concomitant use with ritonavir substantially increases ticagrelor exposure which may increase the bleeding risk. In addition, ticagrelor is also a mild CYP3A4 inhibitor and P-gp inhibitor. Ritonavir is a substrate of both CYP3A4 and P-gp. [44951]

Timolol: (Moderate) Timolol is significantly metabolized by CYP2D6 isoenzymes. CYP2D6 inhibitors, such as ritonavir, may impair timolol metabolism; the clinical significance of such interactions is unknown. [5044] [5270]

Tinidazole: (Moderate) Coadministration of tinidazole with ritonavir may accelerate the elimination of tinidazole, decreasing the plasma concentration of tinidazole, or prolong the half-life and decrease the plasma clearance of tinidazole, increasing the plasma concentration of tinidazole. Tinidazole is a CYP3A4 substrate, and ritonavir is a CYP3A4 inhibitor and strong CYP3A4 inducer. [28315] [29931] [47165]

Tiotropium; Olodaterol: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28318] [28341] [32901] [33925] [41231] [65157] [65170] (Moderate) Beta-agonists, such as olodaterol, may be associated with adverse cardiovascular effects including QT interval prolongation. Beta-agonists should be administered with extreme caution to patients being treated with drugs known to prolong the QT interval because the action of beta-agonists on the cardiovascular system may be potentiated. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with olodaterol include ritonavir. [47165] [57710]

Tofacitinib: (Major) A dosage reduction of tofacitinib is necessary if coadministered with ritonavir. In patients receiving 5 mg twice daily, reduce to 5 mg once daily; in patients receiving 10 mg twice daily, reduce to 5 mg twice daily; in patients receiving 11 mg once daily of the extended-release formulation, switch to the immediate-release formulation at a dose of 5 mg once daily. Tofacitinib exposure is increased when coadministered with ritonavir. Ritonavir is a strong CYP3A4 inhibitor; tofacitinib is a CYP3A4 substrate. Coadministration with another strong CYP3A4 inhibitor increased tofacitinib exposure by 2-fold. [28315] [52315]

Tolterodine: (Major) Avoid coadministration of lopinavir with tolterodine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid

any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Tolerodine has been associated with dose-dependent prolongation of the QT interval, especially in poor CYP2D6 metabolizers. [28341] [31112] [65157] [65170] (Major) Reduce the dose of immediate-release tolterodine to 1 mg twice daily and extended-release tolterodine to 2 mg once daily if coadministered with ritonavir. Concurrent use may increase tolterodine exposure. ritonavir is a strong CYP3A4 inhibitor. In CYP2D6 poor metabolizers, the CYP3A4 pathway becomes important in tolterodine elimination. Because it is difficult to assess which patients will be poor CYP2D6 metabolizers, reduced doses of tolterodine are advised when administered with strong CYP3A4 inhibitors. In a drug interaction study, coadministration of a strong CYP3A4 inhibitor increased the tolterodine AUC by 2.5-fold in CYP2D6 poor metabolizers. [31112] [43295] [47165]

Tolvaptan: (Severe) The concomitant use of tolvaptan and ritonavir is contraindicated. Concurrent use is expected to increase tolvaptan exposure. Tolvaptan is a sensitive CYP3A4 substrate; ritonavir is a strong inhibitor of CYP3A4. Coadministration of another strong CYP3A4 inhibitor increased tolvaptan exposure 5-fold. No data exists regarding the appropriate dose adjustment needed to allow safe administration of tolvaptan with strong CYP3A4 inhibitors. [35780] [47165] [63106]

Topiramate: (Moderate) Concurrent administration of topiramate with ritonavir may result in decreased concentrations of ritonavir. Topiramate is not extensively metabolized, but is a mild CYP3A4 inducer. Ritonavir is metabolized by this enzyme. Caution and close monitoring are advised if these drugs are administered together. [28378] [57036] [58664]

Topotecan: (Major) Avoid coadministration of ritonavir with oral topotecan due to increased topotecan exposure; ritonavir may be administered with intravenous topotecan. Oral topotecan is a substrate of P-glycoprotein (P-gp) and ritonavir is a P-gp inhibitor. Oral administration within 4 hours of another P-gp inhibitor increased the dose-normalized AUC of topotecan lactone and total topotecan 2-fold to 3-fold compared to oral topotecan alone. [28380] [33536] [33578] [46322]

Toremifene: (Major) Avoid coadministration of lopinavir; ritonavir with toremifene due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir; ritonavir is associated with QT prolongation. Toremifene has been shown to prolong the QTc interval in a dose- and concentration-related manner. [28341] [28822] [65157] [65170] (Major) Avoid coadministration of ritonavir with toremifene if possible due to increased plasma concentrations of toremifene which may result in QT prolongation. If concomitant use is unavoidable, closely monitor ECGs for QT prolongation and monitor electrolytes; correct hypokalemia or hypomagnesemia prior to administration of toremifene. Toremifene is a CYP3A4 substrate that has been shown to prolong the QTc interval in a dose- and concentration-related manner, and ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor increased toremifene exposure by 2.9-fold; exposure to N-demethyltoremifene was reduced by 20%. [28822] [47165]

Trabectedin: (Major) Avoid the concomitant use of trabectedin with ritonavir due to the risk of increased trabectedin exposure. Trabectedin is a CYP3A substrate and ritonavir is a strong CYP3A inhibitor. Coadministration with another strong CYP3A inhibitor increased the systemic exposure of a single dose of trabectedin (0.58 mg/m² IV) by 66% compared to a single dose of trabectedin (1.3 mg/m²) given alone. [47165] [60248]

Tramadol: (Major) Tramadol is primarily metabolized by CYP2D6 and CYP3A4; drugs that inhibit these enzymes, such as ritonavir, may decrease the metabolism of tramadol. This may result in a decreased concentration of the active metabolite (O-desmethyltramadol) leading to decreased analgesic effects and possibly increased side effects (seizures and serotonin syndrome) due to higher tramadol concentrations. [40255] [5043] [9316]

Trandolapril; Verapamil: (Moderate) Concurrent administration of verapamil with ritonavir may result in elevated plasma concentrations of both drugs. Both verapamil and ritonavir are substrates and inhibitors of CYP3A4. Verapamil also inhibits the drug transporter P-glycoprotein (P-gp); ritonavir is a substrate of P-gp. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [11554] [40025] [5044] [56565] [6446]

Trazodone: (Major) Avoid coadministration of lopinavir with trazodone due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Trazodone can prolong the QT/QTc interval at therapeutic doses. In addition, there are postmarketing reports of torsade de pointes (TdP). [28341] [38831] [65157] [65170] (Major) Avoid coadministration of trazodone with ritonavir due to the potential for increased trazodone exposure and associated adverse effects including QT prolongation. If concurrent use cannot be avoided, consider a reduced dose of trazodone based on tolerability. Trazodone is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration of other strong CYP3A4 inhibitors increased the exposure of trazodone compared to the use of trazodone alone. [28315] [38831] [46638] [47165]

Triamcinolone: (Moderate) Ritonavir may inhibit the CYP3A4 metabolism of triamcinolone, resulting in increased plasma triamcinolone concentrations and reduced serum cortisol concentrations. There have been reports of clinically significant drug interactions in patients receiving ritonavir (a strong CYP3A4 inhibitor) along with corticosteroids resulting in systemic corticosteroid effects including, but not limited to, Cushing syndrome and adrenal suppression. Consider the benefit-risk of concomitant use and monitor for systemic corticosteroid side effects. Consider using an alternative treatment to triamcinolone, such as a corticosteroid not metabolized by CYP3A4 (i.e., beclomethasone or prednisolone). In some patients, a corticosteroid dose adjustment may be needed. If corticosteroid therapy is to be discontinued, consider tapering the dose over a period of time to decrease the potential for withdrawal. [28341] [47165] [56202]

Triazolam: (Severe) Coadministration of triazolam, a primary CYP3A4 substrate, with strong CYP3A4 inhibitors, such as protease inhibitors, is contraindicated by the manufacturer of triazolam due to the risk for increased and prolonged sedation and respiratory depression. Concurrent use is expected to produce large increases in systemic exposure to triazolam, with the potential for serious adverse effects. [28142] [28341] [28731] [28839] [28995] [29012] [31320] [32432] [41543] [46638] [47165]

Tricyclic antidepressants: (Major) Avoid coadministration of lopinavir with tricyclic antidepressants (TCAs) due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of

subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. TCAs share pharmacologic properties similar to the Class IA antiarrhythmic agents and may prolong the QT interval, particularly in overdose or with higher-dose prescription therapy (elevated serum concentrations). [28225] [28341] [28415] [28416] [65157] [65170] (Moderate) A dose reduction of the tricyclic antidepressant (TCA) may be necessary when coadministered with ritonavir. Concurrent use may result in elevated TCA plasma concentrations. [47165]

Trifluoperazine: (Major) Avoid coadministration of lopinavir with trifluoperazine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Trifluoperazine is associated with a possible risk for QT prolongation. [28341] [28415] [65157] [65170]

Trimetrexate: (Moderate) Protease inhibitors inhibit the cytochrome P450 3A4 isoenzyme. Concurrent administration of trimetrexate with protease inhibitors may result in increased trimetrexate levels. Monitor patients closely. [4718] [5172] [5206] [5224]

Trimipramine: (Moderate) A dose reduction of the tricyclic antidepressant (TCA) may be necessary when coadministered with ritonavir. Concurrent use may result in elevated TCA plasma concentrations. [47165]

Triptorelin: (Major) Avoid coadministration of lopinavir with triptorelin due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Androgen deprivation therapy (i.e., triptorelin) may prolong the QT/QTc interval. [28341] [45411] [65157] [65170]

Ubrogepant: (Severe) Coadministration of ubrogepant and ritonavir is contraindicated as concurrent use may increase ubrogepant exposure and the risk of adverse effects. Ubrogepant is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor resulted in a 9.7-fold increase in the exposure of ubrogepant. [47165] [64874]

Ulipristal: (Moderate) Use of ulipristal and ritonavir may increase the plasma concentration of ulipristal but is not likely to be significant for emergency contraceptive use. Avoid ritonavir if ulipristal is given chronically for hormonal conditions. Ulipristal is a substrate of CYP3A4 and ritonavir is a potent CYP3A4 inhibitor and in chronic use, may induce CYP3A4. Use together is likely to increase ulipristal concentrations overall, which may increase the risk for ulipristal-related adverse reactions. [41569] [50623]

Umeclidinium; Vilanterol: (Major) Avoid coadministration of lopinavir with long-acting beta-agonists due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses, when associated with hypokalemia, or when used with other drugs known to prolong the QT interval. This risk may be more clinically significant with long-acting beta-agonists as compared to short-acting beta-agonists. [28318] [28341] [32901] [33925] [41231] [65157] [65170]

Upadacitinib: (Moderate) Use upadacitinib with caution in patients receiving chronic treatment with ritonavir as upadacitinib exposure and adverse effects may be increased. Upadacitinib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. Concurrent use of upadacitinib with a strong inhibitor increased upadacitinib exposure by 75%. [47165] [64572]

Valbenazine: (Major) The dose of valbenazine should be reduced to 40 mg once daily during co-administration with a strong CYP3A4 inhibitor, such as ritonavir. QT prolongation is not clinically significant at valbenazine concentrations expected with recommended dosing; however, valbenazine concentrations may be higher in patients taking a strong CYP3A4 inhibitor and QT prolongation may become clinically significant. [61873]

Valproic Acid, Divalproex Sodium: (Major) In a single case report, possible ritonavir-mediated induction of valproic acid glucuronidation resulted in a decrease in valproic acid concentrations and efficacy. A man with bipolar disorder and HIV was stabilized on valproic acid 250 mg PO three times daily. Treatment was started with lopinavir; ritonavir and lamivudine, 3TC; zidovudine, ZDV in addition to the valproic acid. Three weeks after starting the antiretroviral medication, his manic symptoms worsened. Upon hospital admission due to the mania, his valproic acid concentration had decreased 48% (from 495 to 238 micromol/l). His valproic acid dose was increased to 1500 mg and olanzapine was introduced. The valproic acid concentration following this dose escalation was 392 micromol/l, and the patient improved clinically. Of note, the patient had also received paroxetine for treatment of comorbid depression when the antiretrovirals were initiated, but the SSRI was discontinued by the patient after 5 days. The SSRI may have contributed to the initial hypomanic episode. Clinicians should be aware of this potential interaction and closely monitor valproic acid concentrations and efficacy. A valproic acid dose increase may be needed. In addition, valproic acid is an inducer of P-glycoprotein (P-gp) and an inhibitor/inducer of CYP3A4; ritonavir is a substrate of both CYP3A4 and P-gp. [57048] [57080] [8650]

Valsartan: (Moderate) Concurrent use of lopinavir with valsartan may result in elevated valsartan serum concentrations. Valsartan is a substrate for the drug transporter organic anion transporting polypeptide (OATP1B1/1B3); lopinavir is an OATP1B1 inhibitor. Monitor for increased toxicities if these drugs are given together. [56575] [61510] [61511] [61513] (Minor) Valsartan is a substrate of the hepatic efflux transporter MRP2 and ritonavir is an inhibitor of MRP2. Coadministration may increase systemic exposure to valsartan. Patients should be monitored for adverse effects of valsartan during coadministration. [28315] [29130] [36646] [39870] [60860]

Vandetanib: (Major) Avoid coadministration of lopinavir with vandetanib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Interrupt or dose reduce vandetanib if QT prolongation occurs. Vandetanib can prolong the QT interval in a concentration-dependent manner; torsade de pointes (TdP) and sudden death have been reported in patients receiving vandetanib. Lopinavir is associated with QT prolongation. [28341] [43901] [65157] [65170]

Vardenafil: (Major) Avoid coadministration of lopinavir with vardenafil due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs are associated with QT prolongation. [28216] [28341] [41124]

[\[46638\]](#) [\[65157\]](#) [\[65170\]](#) (Major) Do not use vardenafil orally disintegrating tablets with ritonavir due to increased vardenafil exposure; do not exceed a single dose of 2.5 mg per 72-hour period of vardenafil oral tablets. Vardenafil is primarily metabolized by CYP3A4/5; ritonavir is a strong CYP3A4 inhibitor. Coadministration of ritonavir with vardenafil resulted in a 49-fold increase in vardenafil AUC and a 13-fold increase in vardenafil C_{max}. Concomitant use may increase the risk of vardenafil-related adverse effects, such as prolonged erection or QT prolongation. [\[28216\]](#) [\[41124\]](#) [\[46638\]](#) [\[47165\]](#)

Vemurafenib: (Major) Avoid coadministration of lopinavir with vemurafenib due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs have been associated with QT prolongation. [\[28341\]](#) [\[45335\]](#) [\[56579\]](#) [\[65157\]](#) [\[65170\]](#) (Major) Avoid coadministration of vemurafenib with ritonavir due to the potential for increased vemurafenib exposure; replace these drugs with alternative agents when possible. Vemurafenib is a substrate of CYP3A4; coadministration of a strong CYP3A4 inhibitor like ritonavir may increase vemurafenib plasma concentrations and may lead to increased toxicity. [\[45335\]](#) [\[47165\]](#)

Venetoclax: (Major) Coadministration of ritonavir with venetoclax is contraindicated during the initiation and ramp-up phase in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL); consider an alternative medication or adjust the venetoclax dose with close monitoring for toxicity (e.g., hematologic toxicity, GI toxicity, and tumor lysis syndrome) in patients receiving a steady daily dose of venetoclax if concurrent use is necessary. In patients with acute myeloid leukemia (AML), reduce the venetoclax dose and monitor for toxicity during concurrent use. Resume the original venetoclax dose 2 to 3 days after discontinuation of ritonavir. Specific venetoclax dosage adjustments are as follows: CLL/SLL patients at steady daily dose: 100 mg/day. AML patients: 10 mg on day 1, 20 mg on day 2, 50 mg on day 3, then 100 mg/day starting on day 4. Coadministration of ritonavir, a strong CYP3A, P-gp, and OATP1B1/B3 inhibitor increased the venetoclax AUC by 690% in a drug interaction study. [\[47165\]](#) [\[60706\]](#)

Venlafaxine: (Major) Avoid coadministration of lopinavir with venlafaxine due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Venlafaxine administration is associated with a possible risk of QT prolongation; torsade de pointes (TdP) has reported with postmarketing use. [\[10568\]](#) [\[28275\]](#) [\[28341\]](#) [\[65157\]](#) [\[65170\]](#)

Verapamil: (Moderate) Concurrent administration of verapamil with ritonavir may result in elevated plasma concentrations of both drugs. Both verapamil and ritonavir are substrates and inhibitors of CYP3A4. Verapamil also inhibits the drug transporter P-glycoprotein (P-gp); ritonavir is a substrate of P-gp. Ritonavir also prolongs the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. [\[11554\]](#) [\[40025\]](#) [\[5044\]](#) [\[56565\]](#) [\[6446\]](#)

Vilazodone: (Major) Because CYP3A4 is the primary isoenzyme involved in the metabolism of vilazodone, the manufacturer of vilazodone recommends that the daily dose not exceed 20 mg/day during concurrent use of a strong CYP3A4 inhibitor, such as ritonavir. The original vilazodone dose can be resumed when the CYP3A4 inhibitor is discontinued. [\[28315\]](#) [\[43177\]](#)

Vinblastine: (Major) Ritonavir is an inhibitor of the efflux transporter P-glycoprotein (P-gp, ABCB1) and an inhibitor of cytochrome P450 (CYP) isoenzyme 3A4. Vinblastine is a P-gp and CYP3A4 substrate. Increased concentrations of vinblastine are likely if it is coadministered with ritonavir; exercise caution. [\[28341\]](#) [\[28380\]](#) [\[34653\]](#) [\[34655\]](#) [\[47165\]](#) [\[56579\]](#) [\[57949\]](#) [\[59581\]](#)

Vincristine Liposomal: (Major) The plasma concentrations of vincristine may be significantly elevated when administered concurrently with protease inhibitors. Consideration should be given to temporarily withholding the regimen in patients who develop significant hematological or gastrointestinal toxicity when protease inhibitors are coadministered with vincristine. Vincristine is a CYP3A4 and P-glycoprotein (P-gp) substrate; protease inhibitors are CYP3A4 inhibitors and some also inhibit P-gp. If the antiretroviral regimen needs to be withheld for a prolonged period, consider use of a revised regimen that does not include a CYP3A4 and P-gp inhibitor. [\[28155\]](#) [\[28498\]](#) [\[28731\]](#) [\[29472\]](#) [\[31320\]](#) [\[32432\]](#) [\[34654\]](#) [\[34655\]](#) [\[34656\]](#) [\[47165\]](#) [\[49123\]](#) [\[50768\]](#) [\[50769\]](#) [\[51080\]](#) [\[51432\]](#) [\[57949\]](#)

Vincristine: (Major) The plasma concentrations of vincristine may be significantly elevated when administered concurrently with protease inhibitors. Consideration should be given to temporarily withholding the regimen in patients who develop significant hematological or gastrointestinal toxicity when protease inhibitors are coadministered with vincristine. Vincristine is a CYP3A4 and P-glycoprotein (P-gp) substrate; protease inhibitors are CYP3A4 inhibitors and some also inhibit P-gp. If the antiretroviral regimen needs to be withheld for a prolonged period, consider use of a revised regimen that does not include a CYP3A4 and P-gp inhibitor. [\[28155\]](#) [\[28498\]](#) [\[28731\]](#) [\[29472\]](#) [\[31320\]](#) [\[32432\]](#) [\[34654\]](#) [\[34655\]](#) [\[34656\]](#) [\[47165\]](#) [\[49123\]](#) [\[50768\]](#) [\[50769\]](#) [\[51080\]](#) [\[51432\]](#) [\[57949\]](#)

Vinorelbine: (Moderate) Monitor for an earlier onset and/or increased severity of vinorelbine-related adverse reactions, including constipation and peripheral neuropathy, if coadministration with ritonavir is necessary. Vinorelbine is a CYP3A4 substrate and ritonavir is a strong CYP3A4 inhibitor. [\[47165\]](#) [\[56871\]](#)

Vorapaxar: (Major) Avoid coadministration of vorapaxar and ritonavir. Increased serum concentrations of vorapaxar are possible when vorapaxar, a CYP3A4 substrate, is coadministered with ritonavir, a strong CYP3A inhibitor. Increased exposure to vorapaxar may increase the risk of bleeding complications. [\[57151\]](#)

Voriconazole: (Major) Avoid coadministration of lopinavir with voriconazole due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Voriconazole has been associated with QT prolongation and rare cases of torsade de pointes. [\[28158\]](#) [\[28341\]](#) [\[46638\]](#) [\[54713\]](#) [\[65157\]](#) [\[65170\]](#) (Major) Coadministration of voriconazole and ritonavir at doses of 400 mg every 12 hours is contraindicated, and coadministration of voriconazole with ritonavir at doses of 100 mg should be avoided unless an assessment of the benefit to risk ratio justifies concurrent use. In one study, concurrent administration of voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 8 days) and ritonavir (400 mg every 12 hours for 9 days) resulted in a 66% and 82% decrease in voriconazole C_{max} and AUC, respectively. Low dose

ritonavir (100 mg every 12 hours) decreased voriconazole Cmax and AUC concentrations by 24% and 39%, respectively. [28158] [28315] [46638] [47165]

Vorinostat: (Major) Avoid coadministration of lopinavir with vorinostat due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Both drugs are associated with QT prolongation. [28341] [32789] [65157] [65170] (Major) The use of ritonavir could result in QT prolongation. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with ritonavir include vorinostat. [32789] [47165]

Voxelotor: (Major) Avoid coadministration of voxelotor and ritonavir as concurrent use may increase voxelotor exposure and lead to increased toxicity. If coadministration is unavoidable, reduce voxelotor dosage to 1,000 mg PO once daily. Voxelotor is a substrate of CYP3A4; ritonavir is a strong CYP3A4 inhibitor. Coadministration with another strong CYP3A4 inhibitor is predicted to increase voxelotor exposure by 42% to 83%. [47165] [64778]

Warfarin: (Major) Many antiretroviral agents may interact with warfarin. Agents that inhibit cytochrome P450 (CYP) isoenzymes 3A4, 1A2, or 2C9 may decrease the metabolism of warfarin leading to increased anticoagulation effects. Ritonavir may have induction or inhibition effects on warfarin metabolism. When warfarin (single dose of 5 mg) is administered with ritonavir (400 mg every 12 hours) a 9% increase in warfarin AUC and a 9% decrease in warfarin Cmax is seen. The high vitamin E content in amprenavir formulations may exacerbate the effects of warfarin. Patients should be carefully monitored for changes in INR, with the potential need for warfarin dosage adjustments, if warfarin and antiretroviral agents are coadministered. [28142] [28549] [46638]

Yohimbine: (Moderate) Concurrent administration of yohimbine with ritonavir may result in elevated yohimbine plasma concentrations. Yohimbine is metabolized by the hepatic isoenzymes CYP3A4 and CYP2D6; ritonavir is an inhibitor of these enzymes. Caution and close monitoring are advised if these drugs are administered together. [42997] [57066] [58664]

Zafirlukast: (Moderate) Concurrent administration of zafirlukast with ritonavir may result in elevated plasma concentrations of ritonavir. In vitro, zafirlukast is an inhibitor of the hepatic isoenzyme CYP3A4. Ritonavir is a substrate for CYP3A4. Caution and close monitoring are advised if these drugs are administered together. [2129] [28222] [58664] [7806] [9700]

Zalcitabine, ddC: (Major) Zalcitabine may cause peripheral neuropathy and coadministration with other drugs associated with peripheral neuropathy, such as ritonavir, should be avoided when possible. [1800] [6580]

Zaleplon: (Moderate) Zaleplon is partially metabolized by CYP3A4, and concurrent use of strong CYP3A4 inhibitors, such as ritonavir, may decrease the clearance of zaleplon. Routine dosage adjustments of zaleplon are not required. Dosage adjustments should be made on an individual basis according to efficacy and tolerability. [29887]

Zanubrutinib: (Major) Decrease the zanubrutinib dose to 80 mg PO once daily if coadministered with ritonavir. Coadministration may result in increased zanubrutinib exposure and toxicity (e.g., infection, bleeding, and atrial arrhythmias). Interrupt zanubrutinib therapy as recommended for adverse reactions. After discontinuation of ritonavir, resume the previous dose of zanubrutinib. Zanubrutinib is a CYP3A4 substrate; ritonavir is a strong CYP3A4 inhibitor. The AUC of zanubrutinib was increased by 278% when coadministered with another strong CYP3A4 inhibitor. [47165] [64748]

Zidovudine, ZDV: (Minor) Since ritonavir induces glucuronidation, there is the potential for reduction in zidovudine, ZDV plasma concentrations during concurrent therapy with ritonavir. When coadministered with ritonavir, the AUC and Cmax of zidovudine, ZDV are decreased by 12% and 27%. The clinical significance of this interaction is unknown. [28315] [47165] [58664]

Zileuton: (Moderate) Concurrent administration of zileuton with protease inhibitors may result in elevated zileuton plasma concentrations. Zileuton is metabolized by the hepatic isoenzyme CYP3A4; protease inhibitors block this enzyme. Caution and close monitoring are advised if these drugs are administered together [34597] [34598] [51119]

Ziprasidone: (Major) Avoid coadministration of lopinavir with ziprasidone due to the potential for additive QT prolongation. If use together is necessary, obtain a baseline ECG to assess initial QT interval and determine frequency of subsequent ECG monitoring, avoid any non-essential QT prolonging drugs, and correct electrolyte imbalances. Lopinavir is associated with QT prolongation. Clinical trial data indicate that ziprasidone causes QT prolongation; there are postmarketing reports of torsade de pointes (TdP) in patients with multiple confounding factors. [28233] [28341] [65157] [65170] (Major) Concomitant use of ziprasidone and ritonavir should be avoided due to the potential for additive QT prolongation. Clinical trial data indicate that ziprasidone causes QT prolongation; there are postmarketing reports of torsade de pointes (TdP) in patients with multiple confounding factors. The use of ritonavir could result in QT prolongation. In addition, the plasma concentrations of ziprasidone may be elevated when administered concurrently with ritonavir. Clinical monitoring for adverse effects, such as extrapyramidal symptoms and CNS effects, is recommended during coadministration. Ritonavir is a strong CYP3A4 inhibitor and ziprasidone is a partial CYP3A4 substrate. Coadministration of another strong CYP3A4 inhibitor increased the AUC and Cmax of ziprasidone by about 35 to 40%. [28233] [47165]

Zolmitriptan: (Moderate) Concurrent administration of zolmitriptan with ritonavir may result in elevated zolmitriptan plasma concentrations. Zolmitriptan is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are administered together. [57037] [58664]

Zolpidem: (Moderate) Consider decreasing the dose of zolpidem if coadministration with protease inhibitors is necessary. Zolpidem is a CYP3A4 substrate and protease inhibitors are strong CYP3A4 inhibitors. Coadministration with strong CYP3A4 inhibitors increased the AUC of zolpidem by 34% to 70%. [28001] [28315] [32432] [57789]

Zonisamide: (Moderate) Concurrent administration of zonisamide with ritonavir may result in elevated plasma concentrations of both zonisamide and ritonavir. Zonisamide is metabolized by the hepatic isoenzyme CYP3A4; ritonavir is an inhibitor of this enzyme. Additionally, zonisamide is a weak inhibitor of P-gp, and ritonavir is a substrate of P-gp. There is theoretical potential for zonisamide to affect the pharmacokinetics of drugs that are P-gp substrates. Use caution when starting or stopping zonisamide or changing the

zonisamide dosage in patients also receiving drugs which are P-gp substrates. Caution and close monitoring are advised if these drugs are administered together. [28843] [58664]

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Monitoring Parameters

- blood glucose
- CBC with differential
- CD4+ T cell count
- hepatitis B serology
- LFTs
- plasma hepatitis C RNA
- plasma HIV RNA
- pregnancy testing
- serum bilirubin (total and direct)
- serum cholesterol
- serum lipid profile
- urinalysis

US Drug Names

- Kaletra

Global Drug names

Argentina

- Kaletra - (Abbott)

Australia

- Kaletra - (AbbVie)

Austria

- Kaletra - (AbbVie)

Belgium

- Kaletra - (AbbVie)

Brazil

- Kaletra - (AbbVie)

Canada

- Kaletra - (AbbVie)

Chile

- Kaletra - (Abbott)

China

- Aluvia - (Abbott)

Czech Republic

- Kaletra - (AbbVie)

Denmark

- Kaletra - (AbbVie)

Finland

- Kaletra - (AbbVie)

France

- Kaletra - (AbbVie)

Germany

- Kaletra - (AbbVie)

Greece

- Kaletra - (AbbVie)

Hong Kong

- Kaletra - (AbbVie)

Hungary

- Kaletra - (AbbVie)

India

- Emletra - (Emcure)
- Lopimmune - (Cipla)
- Ritomax-L - (Alkem)

Indonesia

- Aluvia - (Abbott)

Ireland

- Kaletra - (AbbVie)

Israel

- Kaletra - (AbbVie)

Italy

- Kaletra - (Abbott)

Japan

- Kaletra - (AbbVie)

Malaysia

- Kaletra - (AbbVie)

Mexico

- Kaletra - (AbbVie)

Netherlands

- Kaletra - (AbbVie)

New Zealand

- Kaletra - (AbbVie)

Norway

- Kaletra - (AbbVie)

Philippines

- Aluvia - (Abbott)

Poland

- Kaletra - (AbbVie)

Portugal

- Kaletra - (AbbVie)

Russian Federation

- Kaletra - (AbbVie)

Singapore

- Kaletra - (AbbVie)

South Africa

- Aluvia - (Abbott)
- Kaletra - (Abbott)

Spain

- Kaletra - (AbbVie)

Sweden

- Kaletra - (AbbVie)

Switzerland

- Kaletra - (AbbVie)

Thailand

- Aluvia - (Zuellig)
- Kaletra - (Abbott)

Turkey

- Kaletra - (AbbVie)

Ukraine

- Aluvia - (AbbVie)
- Kaletra - (AbbVie)

United Kingdom

- Kaletra - (Abbott)

Venezuela

- Kaletra - (Abbott)

- Kalmeltrex - (Cipla)
- Rilopravir - (Biogalenic)

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